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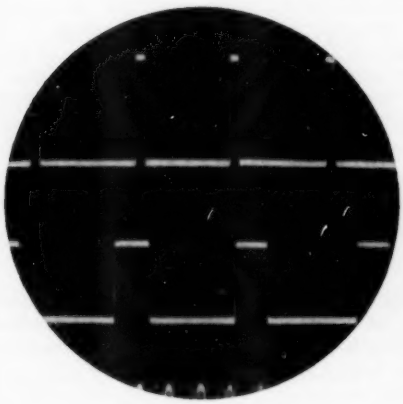

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2. Gerhard Hirschfeld *Journal of Nervous and Mental Diseases* **117**: 323-328, April, 1953.
3. W. T. Liberson *Psychiatric Treatment* Vol. 31 of Proc. A.R.N.M.D. Williams and Wilkins, Baltimore, 1953.

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A NEURAL FRACTIONATING AND COMBINING SYSTEM

RICHARD M. BRICKNER, M.D.
NEW YORK

AMOBARBITAL, like other anesthetics, is usually thought of as causing people to speak "irrational nonsense." However, study shows that the verbal material produced under this drug is just as systematized as any other product of neural activity and can be as readily classified. It is thought that our knowledge of the physiology of mentation might profit by a systematic study of the productions of persons in amobarbital narcosis. Some of the results of such an analysis, derived from over 15,000 pages of material recorded from more than 60 patients in deep amobarbital sleep, are presented in this article.

There appears to be a specifically definable type of mental activity which becomes conspicuous when the brain has been acted upon by a suitable dose of the drug. The relative uniformity of type of utterance strongly suggests one thing, that the portion of the brain organization which does operate during narcosis, or the manner in which it operates, is specific and definable.

For simplicity's sake it will be referred to as a portion of the brain and will be designated as the C-organization (and the mental processes associated with it, the C-mind).* The complete, waking brain, operating in its normal manner, is referred to as the A-organization, and those elements anesthetized or chiefly acted upon by the drug, as the B-organization.

It is important to keep in mind that the drug acts on brain tissue, not on psychological constructs, such as the "ego" or "superego"—a usage some authors employ.

Whatever the ultimate explanation, it is highly improbable that we are dealing with simple anesthesia of such parts as the frontal or temporal lobe as such, because the subjects do not typically behave very much like people with marked impairment of function of either of these lobes. Even so, an occasional remark suggestive of frontal lobe impairment does occur: "Whatever you can do, I can do better." Also, the productions of narcotized patients do not resemble those of senile persons; so

---

Presidential Address, read at a meeting of the New York Neurological Society, Oct. 6, 1953.

From the Neurological Service of the Mount Sinai Hospital; Dr. Morris Bender, Chief Neurologist.

* To be sure, we do not know how the drug exercises its effect on the brain; it may merely alter the manner in which some or all portions of the brain operate, perhaps differentially; conceivably, it anesthetizes some parts, leaving others exposed, but this is probably far too simple an explanation. Whatever the explanation may prove to be, mental activity during narcosis seems to be of a specific type (evaluated according to the verbal utterances of patients). The term C-organization has been selected as being at least generally applicable and useful in alluding to the situation.

the brain parts or processes affected in these states are presumably different. It is conceivable that the drug acts mainly upon certain cortical layers; these may perhaps be largely frontal (Himwich and other students of metabolism).[1]

Of major importance to us, however, is the fact that some networks of the cortex itself clearly do operate even when the brain is deeply narcotized. Moreover, they operate so as to produce repeatedly, predictably, and under planned conditions the specifically definable type of result already mentioned.

The regular demonstration of this fact strongly suggests that this type of mentation bespeaks certain inherent properties of the neural organization, and not simply a pathological process caused by the drug. Further, certain similarities between mental behavior during amobarbital sleep and normal sleep (dreams) suggest that in both instances the behavior results from the same type of brain activity.

The C-organization is presumably at work during normal waking life, influencing all behavior. Also, the C-organization is probably the physiological or anatomical groundwork for the Freudian "unconscious"; however, the total evidence suggests that the "unconscious" aspect is only one among many important qualities of this type of brain function.

FRACTIONATION

One major mode of operation of the C-organization is to separate out and state singly items which ordinarily are grouped or presented in more summarized form. This is simply illustrated by certain examples, such as one patient's response to the inquiry concerning his dreams: "Er, a boat. There's a boat, and water, and a cousin. I don't know whose it was." Another said, "I can do all the things with my ear (?) † that I can do with my mouth and my hands and my mind. . . ." Another, asked what he was dreaming, said, "To be left alone." Q ‡: "Where?" P ‡: "Oh, I don't know. I feel my mother, and my brother, and my sister want to be left alone." One man stated, "Then the member (?) came along—I'm sorry, sir, but you'll have to get ready for our Boston line, which leaves 8, 9, 10, 11 . . ." Another patient said, "I just feel mu . . . this all day because I was told to come at five-thirty, and I gave up a lot of other things I wanted to do at five-thirty . . . and four . . . three (?)-thirty." In another instance the patient took an integrated phrase he heard and broke it into separate items: Q: "Vigorous head nodding. Sleepy?" P.: "Yes." Q.: "Vigorous head nodding." P: "I shouldn't be able to vigorous head nod."

These statements in which items are listed in separated form could, of course, directly reflect the way the items are stored in the brain; more probably they represent an active process of actually breaking into small parts intellectual units which are stored in more complicated form. We have no proof excluding the first of these as a possibility, but there are certainly many instances of unquestionable breakage of larger intellectual units into smaller parts. In fact, the frequency with which this occurs marks it as one of the characteristic modes of action of the C-organization.

† A question mark in parentheses signifies the typist's doubt that the words were understood exactly.

‡ In the dialogue, Q signifies Questioner, and P signifies Patient, during amobarbital interviews.

This breaking, splitting, separating, or fractionating of intellectual units into smaller parts is manifest in more ways than one. Most simply, fractionating, as we shall term it, is done to words or phrases; however, it is also done to concepts. It may reveal itself in the juxtaposition of unfused fractions seemingly unrelated to each other; oftener, fractions from two different sources are fused into a new whole, each still revealing its separate origin, however.

Fractionating seems to go on almost without cessation, apparently applying itself to all situations which come into contact with the C-organization—in short, it evidently constitutes one of the main, inescapable ways in which the C-organization operates. The effect is striking only with large drug doses.

FRACTIONATION OF WORDS

With Juxtaposition of Unfused Fractions.—The fractionation of intellectual units into two, and sometimes more, parts was first noted by observing what many patients often do with words. Often, words are broken in two and then the fractions are used in various ways; these ways are important in themselves and will be fully discussed. The word is often fractured near the middle, so that two roughly equal parts are produced. Some of the splittings are self-explanatory, as, "Yeah! I mean she goes in the same cate-group-gory as the other microphone I was talking to." One man, when asked "Where has she been?," answered, "Probably under eth-am . . . under ether, under Amytal."

With Fusing of Fractions.—The simplest instances of separating and then recombining or fusing the word parts are those in which patients cut common prefixes or suffixes from one word and then combine them with another, often with a result of unusually clear meaning. Examples are: "His decidal to return"; "you mean physiologically difficult because certain centers just . . . disoperate"; "well, I say this is a peculiar room, period; but I don't find it dislikeful at all"; "not that I advocate it, because it indecapacitates you for an awful long time."

Sometimes the exact meaning of these combinations is less certain; yet *a* meaning—perhaps of modern "impressionistic" variety, possibly one C-mind speaking to another—is conveyed. One such was, "This little mound disappears . . . this little mound of tuplips."

The examples we have thus far been using are, of course, usually called slips of the tongue or condensations. However, these "slips" are not occasional and accidental; they are almost incessant, and they plainly express a characteristic and major mode of operation of the C-organization rather than something fortuitous.

Some patients explained to the examiner as they went along, serving in a way as a "Rosetta stone," in the interpretation of their fractionations and fusions. Many of the examples were rather memorable, such as: P: "Yes, I heard you. I'm trying to think. Find it obsiden." Q: "What's that?" P: "Well, obscure, absurd, and hidden from view." In another session the same man said, "The next time I see him I can give him an eager lily . . . tiger lily . . . eager lily is a condensation between Easter and tiger." Another patient said, "I was losing pustomers." Q: "Pustomers? What's that?" P: "Halfway between posters and customs." And, Q: "Why? Have I changed?" P: "You have changed, yes." Q: "What am I like?" P: "Ludicrat."

Twoness.—The meaning relating to the fractioning of things into two parts is probably expressed in another way; the number "two" comes up far oftener than

any other number, and in such special, pointed ways that it must have more than accidental or coincidental significance. There are many instances in which it seems that the number two need not have been mentioned at all, unless it was because the number itself was the important thing—for example, not that the remark is about people, of whom there happened to be two, but that there were two of something, which happened to be people. One patient threw this into relief by using "two" where "double" would have been the conventional and comfortable word. Q: "Go to sleep, Earl." P: "Wait a few minutes (?) . . . let me take my jacket off . . . two-breasted jacket." Random samples from a great many follow: Q: "Tell me what you are thinking." P: "I was thinking about a lot of things, but . . . ." Q: "But what?" P: "Two of them came really to my mind." Q: "Tell me about them." P: "Science and the sun." Also, Q: "What are you dreaming about?" P: "It was only home view and . . . ." Q: "It was only what?" P: "Only two of you . . . dreaming process." Also, "I said I spend two cars of going." Another man said: "Arthur B. had a car. It's interesting, the extent to which I've identified the two of them, namely, the car and Arthur." Another stated: "Then they come down and fix the rest of my . . . ." Q: "Then they come down and fix the rest of my what?" P: "Doodworiee (or Budoir) . . . I don't know any more unless it's the number two."

FRACTIONATING AND COMBINING OF CONCEPTS

Fractionating.—The fractionating process applies to concepts as well as words (this may even have been the case with some of the examples already given). One patient said: "Just like you are now. It was a long time back. I guess I didn't dream of it; I guess I was awake. A long time back." Q: "A long time back?" P: "It wasn't so long; it was back." And P: "He does more harm in the Far East for the cause of the United Nations and the United States than any other single, suitable statesman." Q: "[Repeats] Well, anything at all come to your mind?" P: "Just a . . . a picture of the place where . . . where I get a lot of Amytal. I guess that's silly." Q: "Just a picture of the place, I guess, where I get a lot of Amytal. P: "A picture of an armory" (injections were habitually given into arm veins).

Somewhat more complicated examples are one patient's statement: "It's probably for the simple reason that, well, people who are included in it are people who have no or struggling sexuality." Q: "No or what sexuality?" P: "Struggling." Q: "Who have no struggling sexuality?" P: "Well, no or struggling (?)." And Q: "Yes? Then what?" P: "This little girl (?). . . . I wonder if they objected to me walking in their lines (?)." Q: "What's that, Bert?" P: "Object to me walking in their lines at all." Another said: "By the way, I had a lecture (?) in the moon. So painful a man. I mean the way he . . . I understand he had something severely wrong with him physically. It's painful to get information out of him. I made the remark [yawn] that somebody—it was. . . ."

In an instance composed of still more thoughts, the patient appeared aware of the separation and was unable to prevent it, though she seemed to want to: "For the past five minutes I keep dreaming that it's a dream within a dream . . . . Within a dream. Do you know what I mean? Within a dream, within a dream. About five dreams. . . . I can't quite grasp onto the facts, though." Another, plainly aware of it,

said: "Just a little bit doped up at the moment, but shaking it off quite rapidly. Gosh! My thought continuity is broken each time, and I can't connect one sentence with the one which follows it."

Some of these separatings or fractionatings are suggestive of one of the occasional consequences of frontal lobe injury—conscious inability to hold together separate terms in one's mind. One man who had a frontal lobe tumor found himself no longer adequate in his work of extracting data concerning five critical points from the life insurance policies of certain deceased people and presenting all five points, as a unit, to his superior. He reported that he literally "felt" the points flying apart and simply could not hold them together.[2]

Combining.—As with words, concepts may be combined as well as fractioned. Relatively simple examples are: P: "but I'm tremendously hopeful about being able to study and . . . take advantage of the things I want, take advantage and get to the things I want and can do [murmurs]. What would you call it, an autodeity complex?" And, Q: "What are you dreaming?" P: "Catch a train." Q: "You'll have to . . . ." P: "What time is it?" Q: "It's twenty after, now." P: "I don't remember any of the after-annoyances."

A combination amounting to actual fusion was: P: "How nice that week end would be." Q: "What week end?" P: "When Bill and I were a counselor at camp."

More complex combinations often occur. Frequently they are striking in their use of elements which ordinarily would not be overtly joined. One woman said, "Like malice; the same kind of thing . . . you've got to . . . in the world day after day . . . you might as well be . . . slidier living." A man looked down at the needle in his arm, during the injection, and said, "I like that red-tipped needle; it's very nice." It seemed obvious to the doctor that by "red-tipped" the patient meant the blood, which was visible not on the needle but inside the syringe; yet the patient made a unit of these really distinct elements. Another instance was: P: "I'm just figuring. Is it about an hour yet since I've come out of the Amytal?" Q: "Close to it." P: "What goes on underneath; that's the important thing. Finding out. (?)" Q: "Underneath where?" P: "Underneath that hour. I don't know what goes on." Sometimes a combination is exceedingly pointed in meaning; it is as though the most expressive of all the possible elements of a situation were picked out for combination. One patient with exceedingly mercenary parents declared, "And then she'll say, 'Oh, you son of a dollar.' "

Sometimes there is a sudden, brief alternation between fractioning and combining. One patient said, "There's something there that looks like a heart. And she's trying to put ice in it where it makes that scallop there on the top. She's trying to split it with a piece of wedge-like ice." Q: "Wedge?" P: "Wedgewood." Q: "Wedge what?" P: "Wedge, and it looks as though it were made of ice." Here, the fractioning is plain enough; combining is suddenly introduced with the addition of "wood" to "wedge," forming the seemingly irrelevant combination "Wedgewood." Another said, "Playing the band . . . and the last fellow couldn't even finish the tune because his trombone came apart, and he had to fix it together again (?)." Sometimes it is even hard to be sure of the distinction between fractioning and combining, as in the following example (of which the patient was dimly aware): Q: "What have you been dreaming about?" P: "Labor and vegetable. It doesn't make sense."

Sometimes, as with fractionating, patients recognize that a combining process is going on. One felt words "sticking together." P: "I had to go to Allentown . . . interesting those two words just stick together." Q: "Allentown and what?" P: "S . . . Sonuvabitch."

CONTENT WHICH ACTUALLY SEEMS TO DESCRIBE FRACTIONATING AND COMBINING

Fractionating.—Occasionally, the process of fractionating seems to be actually described in the words used by the patient, suggesting cognizance that he is dividing things into separate elements; sometimes the fractionation as such seems so greatly stressed that is seems to be the major theme of the moment—almost a goal in itself—as, P: "The water is broken up into little partitions; its half-cocked, I meant half cockeyed . . . there's distinction, isn't there?" And, Q: "What was your dream?" P: "Keep Pakistan (?) and the rest of the country separated." Another said, "Got three divergent paths (?)." Q: "Where do they go?" P: "One goes to brown (?) meeting (?); the second goes to wherever it is it's going to and the third goes to hell I suppose." Q: "Well, what are the paths for?" P: "Oh, those are paths in a little fantasy I was having about the cover of a magazine." Q: "Tell me more about that fantasy." P: "One is going out to play basketball or football; the third is going out just not to play."

Combining.—As with fractionation, patients sometimes use terms which seem to describe the combining process, possibly, again, implying a cognizance of it. This has already been illustrated above, in exemplifying something else. Other instances are: "I'm not sure; I'm trying to make it up of elements I know, and it isn't . . . it tastes like hard-boiled eggs dusted with onion salt; my apologies to you and so forth; they had other more standard sandwiches under Cellophane." In one instance the patient said: "I had one picture of a stack of packages of what I think was Knox's Gelatine [laugh]." Q: "Knox's Gelatine?" P: "One pack after, one pack on top of another. Two parallel stacks." Another patient said, "I dreamt of a . . . German maids we have singing th . . . colliding lyrics to another song."

FUNCTIONS OF THE C-ORGANIZATION

As already stated, the C-organization is presumed to be always present and always at work during the normal waking state, although its operations are mainly concealed by the full operations of the complete brain (the C-processes are visible only when they occasionally slip through, or when the person is in a special physiological state, such as normal sleep or amobarbital narcosis). If this is so, the C-organization must have functions.

A. Varied Material for Use of the Intellect.—One function in particular is suggested as a major one. The incessant breaking down of words and concepts into fractions and the incessant reuniting of these to form new units, ever changing in composition, indicate that the C-organization is constantly brewing new combinations, new units, for intellectual use.§

§ This is not the place for a discussion of the biological role of intellect, but elsewhere it has been suggested that the intellect has a distinct evolutionary role, to execute with even greater efficiency (not repress) those functions which help the species and the individual to survive. Whatever the biological, basic functions of intellect, the constant reshuffling of material by the C-organization gives it ever new material to work with.

The C-fractions and recombinations are often such as to express meanings with unusual vividness and accuracy. Hence, from a psychological standpoint and from the point of view of vivid and pointed intercommunication between people, the C-organization has, at least, a potentially important function. Most of the combinations do not seem accidentally made; instead, units are brought together to serve a psychological purpose, which is usually intelligible.

Some instances of this vividly descriptive expression from different patients follow; the combining of units drawn from separate but related sources is evident in each: Q: "And what were you thinking about?" P: "I was thinking of the word 'declare' and the word 'defied.'" And, "Ahum, that's a wonderful relaxed feeling that you have up here." Others were: P: "I'm sleepy like a lion." Q: "Sleepy like a what?" P: "I want somebody to sleep with." Q: "Sing to sleep? Is that what you said?" P: "Sleepy . . . lion?" Q: "Sleepy like a what?" P: "I say I'm sleepy like a man who has nobody to sleep with." And P: " . . . about my family (?) . . . well, it's awfully peculiar. I would like best of all if they would all wrap themselves in a suitcase, dark and dismal, and I should leave them in a station somewhere. I just that second seemed to wake up in a hurry." Q: "Oh, just that second seemed to wake up in a hurry." P: "Heard the . . . distant drum of the ladies' party." (Sound of phone conversation in outer office audible for past several minutes.) Q: "Heard the distant drum of the ladies' party?" P: "Well, the murmur. And P: ". . . whole thing fell on . . . night, the er . . . ." Q: "Fell on around what?" P: "Yeah. Around my . . . shoulders. I just couldn't see it." Q: "What was that? . . . that fell there." P: "The fruitless nature of it." Q: "The fruitless nature of what?" P: "Of his dying." Another patient said: "I'm really. I don't think it's fair for you to be . . . not have this thing and look at me and for me to know that I can't look back the way I want to. Nothing goes on bad over the rocks. The sea comes in and the girls get dressed and I can see the bathing suits (?) standing by, and her little breasts flying in the wind like little puffs of bright snow."

Q: "Well, anything else coming up to your thoughts now?" P: "There are several in my being; I don't know whether this applies to my thoughts or not." Q: "Well, all right, what's in your being?" P: "[Yawn] In the southern-most corner of my being, where few people have ever dared tread before. I have felt a woman . . . ."

P: "Oh, you're the doc. You want to take me away, don't you?" Q: "I want to take you away? What do you mean?" P: "You want to take me away so I can talk." Q: "Take you away what?" P: "To my childhood. Let's go. We will go up in my childhood." Q: "And what will we do there?" P: "Reminisce."

Normal A-intellects (the entire intellect of the entire waking A-organization) rarely, if ever, make conscious use of all the C-material. A large proportion of the fractions and their recombinations are customarily shut out from use by the A-organization. From an A-standpoint, most of them do not have the rank of reality, and conscious, overt use of them is avoided.

On the other hand, some patients with schizophrenia speak as though the C-organization had become dominant, its productions seeming to constitute reality and the individual overtly using them. Possibly this group should be classified as

representing one type of schizophrenia. If further study supports this suggestion, the beginnings of a physiological groundwork would be supplied by which to understand the mental aberrations of at least this group of schizophrenics.

Returning to normal A-intellects, they do not shut out C-productions to a uniform degree. Differences in degree of this exclusion are probably linked with differences in grade of mental rigidity, conformity, and originality. Some A-organizations are so constructed that they exclude from recognition every item which does not easily pass through prebuilt "slots" of rigidly specific size and shape. Others allow the passage of more varied C-items, and the balance between A- and C-organizations is still such as to permit a nonpsychotic life to be led.

To be sure, there are degrees of passing through of C-products by some authors and artists which are regarded as signifying genius. These may be among the cases in which it is sometimes so difficult to distinguish between genius and schizophrenia.

The degree to which this large-scale emergence of C-products can occur without the aid of drugs or artificial states otherwise induced warrants study.

B. Varied Material for Reminding, Recognition, and Other Discreet Intellectual Processes.—Fractions can serve as cues for reminiscence or for recognition of objects and people. Knowledge of this is commonplace; what is new is the role as cues of the particular kind of fractions under discussion. An example is that of a man who entered a certain building on a sight-seeing tour while he was slightly drowsy, just after lunch. To the left stood a small group of people, starting out with a guide. The drowsy man was struck by the shape of the posterior half of a man's head, combined with a hearing-aid plug, seen in profile at the edge of the group. He said to himself, "That must be Joe F., and I must avoid paying any attention to his face, as I seem to be recognizing him by a cue and I want to make sure." The recognition proved to be correct.

Events like this occur frequently in the normal waking state as well as in dreams, where people are incessantly being identified by fractional cues.

It is suggested that the employment of fractions to represent or to initiate whole mental acts adds to efficient, physiologically economical use of the brain.

C. Comparison.—One of the most familiar apparent results of the fractionating process is what we ordinarily call comparison. Evidently a human perforce treats most situations by finding in them two things to compare. This is one major way in which persons use the fractionating and recombining process.

This comparing is of obvious survival value to all forms of life. Edible food rather than toxic substances must be chosen; dangerous temperatures must be avoided and safe ones found, etc. Even forms like the ameba, which have no nervous system, must somehow distinguish between what is healthy and what is not; when an ameba has engulfed a particle, it promptly expels it if it is noxious or non-nutritious. All forms must have some system of recognizing too hot, too rough, too much, or too little water pressure, etc. When a nervous system appears, it takes over these distinctions and makes them more complex and varied.

The productions of people under amobarbital have shown many actual comparisons—seemingly more so than those of the normal waking mind. These comparisons often are made in surprising ways, and they may concern aspects of situations which one would not expect to see specified at all, with or without the element of comparison.

Some examples are: Q: "What, Jim?" P: "Trying to think about what I was going to say about my cousin." Q: "Which cousin?" P: "Cousin who wasn't the same cousin you met, was another cousin." And, Q: "Well, Wes . . . what now?" P: "Blank. I wasn't even thinking. I was just thinking about crossing the street. Getting to the other side. Leaving my friends . . . It looks like blueberries for sky. Everything else is black and white." Q: "What are you dreaming now, Wes?" P: "Nothing. It seems as if you thought you would want me . . . prefer me to dream on one side of the book than on the other. I'm dreaming in a book, so to speak, for the moment." And, P: "Oh, once you get in and once you get out. I don't think it that way." And Q: "Dreaming, Kenny?" P: "No; just (?) thinking (?)." Q: "What were you thinking about? Were you thinking about something?" P: "I was thinking about getting home; and the other one I wasn't thinking." And Q: "From the same church?" P: "[Yawn] Yeah." Q: "Another one?" P: "Across the street. The difference was that one was for the blind and the other wasn't." Also Q: "How is he getting along with his wife?" P: "He just got married Sunday and is on his honeymoon. I haven't seen him. He's afraid; he's afraid; he's afraid. I'm afraid, too. Same thing."

P: "English is a little bad, but . . . ." Q: "It's all right. Don't worry about that." P: "Process of trying to go to sleep. This is some of the difficulty that I ran into on Saturday morning. About nine o'clock." Q: "What kind of difficulty?" P: "Like this. Of wanting to go to sleep and yet not being able to . . . [yawn]. I don't understand this."

P: "Depressed because something's wrong or I'm not elated because something's right. I'm just elated that's all, or depressed."

Q: "What was it, Charles?" P: "You asked him to tell you his dreams." Q: "And then?" P: "They're very similar to mine." Q: "And what else, Charles?" P: "He was very similar to me." Q: "Who was it, Charles?" P: "Maybe just another patient, maybe a friend."

Other examples, some of them fairly subtle, are: Q: "What do you say?" P: "Paint. It isn't long enough." Q: "Yes, tell me; speak on, Wes." P: "It seems that paint is getting as scarce like Dr. Livingston." And, "Well, I'll never be ready in a few minutes if I aren't now." Q: "Do you think you can get up and get dressed?" P: "I think I can now if I can in 15 minutes." One patient spoke of the differentiating process itself, rather subtly: Q: "What about your dad?" P: "I can't be more exacting or differentiation." Another said, "He said he'd take me out to dinner and to the show and everything else like that. At one time I told him yes, but then I backed out. When I told him yes, it was good; when I told him no, it was bad." And, "I don't know whether I want to cry or ought to cry." P: "I don't know . . . I know there's a heck of a lot wrong with me, but I know that it's not all wrong with me. I can feel this fuzziness." Q: "What are you dreaming?" P: "I'm more or less the same size as I am now."

Social Meaning of These Comparisons.—One suggestion can be made concerning the social role of such comparison activity which functions in the way just described, with comparisons actually forced on individuals. Fractions are always being formed, and apparently it is necessary to dispose of one or more elements. Thus, when one is confronted with any situation in life, the brain evidently must

find two aspects in it and seemingly must reduce them to one. In actual practice, this amounts to making a comparison. Something is found in every situation about which a comparison is made.

Because of various other biological and cerebral processes, obvious but not requiring discussion here, these comparisons will tend to take certain regular forms; they will, for example, relate themselves to size (bigger, smaller) and value judgments (better, worse; superior, inferior). These categories themselves generate hostile feelings between people and can be socially very disturbing.

Human behavior would possibly be more consonant with human social welfare if there were more insight regarding this matter. It might help to make behavior more objective if people knew that the comparisons they were acting on often had only slight foundation in external reality and were mainly based on a neurophysiological need to find something to compare.

This material contains some obvious implications concerning dream symbolism and distortion; these will be made the subject of another report.

SUMMARY

The verbal productions, signifying mentation of subjects in amobarbital narcosis, are just as systematized and just as readily subject to classification as any other activities of the central nervous system.

The drug acts on neural tissue, not on psychological constructs, like the ego, the superego, etc. The ensuing changes in mentation are the consequence of this pharmacological action upon the central nervous system.

The C-organization is the name assigned to that portion of the brain organization, functioning as it does in amobarbital narcosis, which is responsible for the types of mentation described.

One of the chief functions of the C-organization is the fractioning of units of thought into smaller divisions and the recombining of these fractions into highly varied combinations.

The psychological and social roles of this function are discussed.

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INTRINSIC MECHANISMS IN PERIODIC BREATHING

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PERIODIC * breathing, as it occurs classically in Cheyne-Stokes respiration or in such variants as Biot's breathing, came to be recognized clinically almost at the same time that the early experimental studies on the course and regulation of breathing began to emerge from the physiological laboratories of the 19th century. Then, as now, this dramatic alteration in the usual pattern of breathing demanded explanation in terms of the fundamental physiology of the genesis and control of respiration and has reflected since then the succession of hypotheses and the swings of emphasis and of interest in this sphere.

The experimental basis for a revised concept of the neurophysiology of breathing has recently been established through the analysis of breathing patterns in a total of more than 350 dogs and 50 cats, studied in the normal unanesthetized state, after a series of transections of the brain stem ranging from hypothalamus to medulla, and before and after vagotomy and the injection of a variety of drugs at each of these levels.† In the course of these experiments periodic breathing has almost invariably appeared in one form or another; in nearly a third of all experiments there has developed a clear-cut alternation of breathing and apnea of the general nature of Biot's breathing or Cheyne-Stokes respiration, in circumstances which point clearly to the following explanation of periodic breathing in terms of the basic outline of the neurophysiology of respiration previously enunciated from this laboratory.

I. ORIGIN OF RESPIRATION

The fundamental postulate upon which this analysis of periodic breathing rests, and which has emerged from studies of the more normal types of breathing preceding it, designates the medulla as the site of the underlying rhythm of respiration, developing there independently of extramedullary influences which have in the past been credited with an essential role in the genesis of the respiratory act. This conclusion

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* All breathing is periodic in the physiological sense, for the neurones of inspiration are periodic; i. e., they discharge rhythmically during inspiration and stop during expiration. "Periodic breathing" is employed throughout this paper in its clinical sense, denoting recurring periods of apnea in the sequence of breaths.

† References 1 through 8.

is based upon the primary fact that animals, including dogs, cats, and monkeys, have been prepared by complete transection of the brain stem within the upper reaches of the medulla and have thereafter been subjected to bilateral section of the vagus nerves and, in some cases, to severance of the glossopharyngeal nerves in addition; they have, nevertheless, maintained respiration bearing close affinities to that seen in normal animals, as well as in animals decerebrated at higher levels of the brain stem. These preparations have survived for periods longer than would be expected if the remaining respiratory act were thought to be due to fortuitous circumstances, such

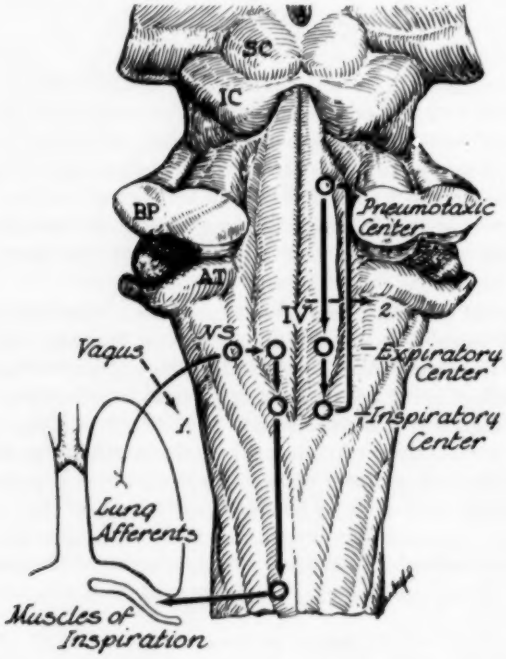

Fig. 1.—Outline drawing of the brain stem of the dog, illustrating earlier hypotheses of the origin of respiration, in which two extramedullary self-activating suppressor circuits are postulated (Pitts[9]). The first, illustrated on the left, invokes the classic concept of the Hering-Breuer reflex, supposedly elicited by stimulation of stretch receptors in the substance of the lungs by their distention during inspiration. These receptors initiate impulses in afferent fibers of the vagus, which are supposed to inhibit further inspiration, presumably via the nucleus solitarius (*NS*) and the expiratory center. The second circuit is illustrated on the right. The inspiratory center is supposed to send impulses rostrally to a "pneumotaxic" center (Pitts[9]) in the upper regions of the pons, which, in turn, relays impulses back to the expiratory center to inhibit inspiration.

Either circuit alone has been supposed to be capable of cycling respiration, but if both were inactivated the inspiratory center was hypothetically incapable of cycling breathing and could produce only a state of sustained inspiration, or "apneusis."

Now it can be affirmed that neither of these circuits is indispensable to the respiratory cycle, but that, as illustrated in Figures *2* and *3*, respiration continues after both vagi and the pons are eliminated by section of the vagi (Arrow *1*) or an appropriate transection of the brain stem between pons and medulla (Arrow *2*). The classical decerebration passes between the superior colliculi (*SC*) and the inferior colliculi (*IC*). The pons occupies the region below the inferior colliculi, and out of it arises the brachia pontis (*BP*). The acoustic tubercles (*AT*) mark the boundary between pons and medulla.

as stimulation from the cut brain stem, etc. Further, in these animals a final section below the obex has invariably led to instantaneous cessation of respiration and death.

Thus, two factors are immediately disposed of which during the past century have been invoked repeatedly as essential to the production of respiratory periodicity, i. e., the vagus nerves and the supramedullary brain stem centers lying in the pons or more rostrally (Pitts [9]). In consequence, neither the Hering-Breuer reflexes by which inspiration, with its consequent lung inflation and afferent bombardment of the medulla via the vagus, was supposed to have inhibited the further continuance of inspiration, nor the so-called pontine pneumotaxic center, which was supposed to have operated via hypothetical nerve circuits between pons and medulla, can be credited, either singly or in cooperation, with imposing upon a supposedly non-periodic medullary discharge the alternating rhythm of inspiration and expiration. Quite to the contrary, the rhythm of respiration continues after both of these factors have been eliminated (Fig. 1). Thus the cause of the rhythmic discharge of respiration must be sought within the medulla itself.

Just how the rhythm of respiration develops within the medulla is still problematical, and it may well be possible that within the confines of the medulla itself anatomical pathways are to be found wherein reciprocating, self-limiting circuits, akin to those postulated between medulla and pons in earlier hypotheses, determine the rhythm of breathing. It is equally possible that some form of autorhythmicity governs the discharge of the cells of the respiratory reticulum not dissimilar to the processes accountable for other autorhythms in the spinal cord and brain stem in which discharge becomes self-limiting by such features as accumulation of positive after-potential, etc.

Neither can it be denied that afferent inflow, from a variety of sources, may play a part in the maintenance of a background of excitation out of which the autorhythm develops, for it must be pointed out that in none of the preparations which form the basis of this study has the respiratory center been entirely deprived of afferent inflow, particularly from the spinal cord. It has been observed frequently that such preparations may become apneic due to hemorrhage, excessive narcosis, etc., and that in such circumstances the respiratory act may be initiated by periodic pinching of the toes, rhythmic compression of the thorax, or other stimulation. The breaths resulting therefrom are the direct reflex consequences of afferent stimulation; this response is true reflex respiration. As the preparation recovers, it is often noted that breaths may continue for some time after stimulation has stopped, as a sort of respiratory after-discharge, and later, after further recovery, spontaneous respiration recommences. It may well be argued that as the respiratory center recovers, the non-specific background of incidental afferent stimulation that comes from receptors throughout the body, from contact with the environment, etc., is adequate to trigger the respiratory discharge. It is perhaps more in keeping with what is known of rhythms in other systems to believe that these stages represent the development of autorhythmicity from low-grade irritability with a simple stimulus-response ratio, through a phase of retained dependence of response upon stimulus, but with multiple response or after-discharge, to fully established autorhythmicity. Such a gradation is clearly seen when isolated nerve fibers are placed in solutions containing abnormally low concentrations of calcium and in cardiac tissue, etc.

II. FUNDAMENTAL RESPIRATORY RHYTHMS

The second consideration essential for the understanding of the mechanism of periodic breathing is the recognition that normal breathing in an intact animal encompasses three distinct respiratory rhythms: (*a*) the rhythm of normal quiet breathing, which may be called eupnea; (*b*) panting, or tachypnea, and (*c*) a slow, deep rhythm of full breaths, which may be called sighing, or all-or-nothing breathing. The first and last of these three are found at the medullary level. Panting has never been seen in the medullary animal in these experiments, although quick repetition of breaths can occur, suggesting that part of the fundamental mechanisms are to be found here.

Eupnea.—Eupnea is preserved in all preparations, however low the level of section, as long as any type of breathing remains, and, like its counterpart in the intact animal, it is of moderate depth and rate and capable of fairly wide variations

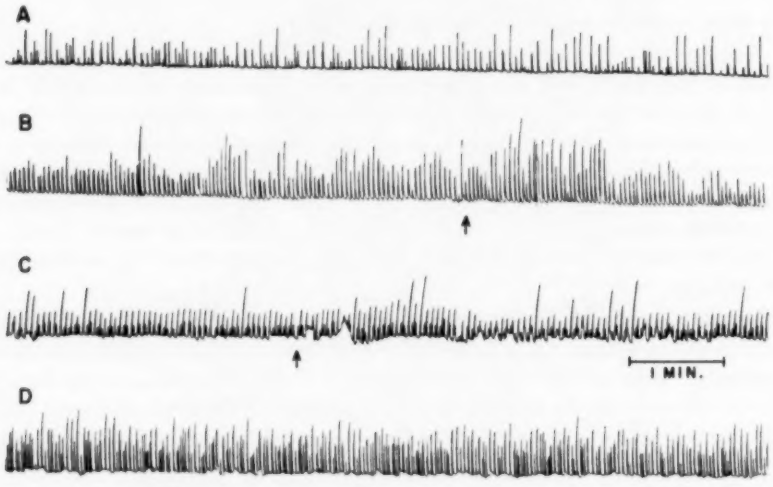

Fig. 2.—*A*, Dog 297-B: medullary transection; vagi intact. *B*, Dog 300-B: medullary transection; vagi sectioned at arrow. *C*, Dog 284-B: medullary transection; vagi sectioned at arrow. *D*, Dog 285-B: medullary transection; vagi previously sectioned.

These records illustrate the "ataxic" character of eupneic respiration in the medullary animal, with almost complete lack of uniformity in amplitude and timing within the limits of normal eupnea. They also document the almost complete absence of any significant influence of vagotomy in the medullary preparation. Inspiration upward.

within limits of both rate and depth. It is clear, however, that neither at its greatest rate does eupnea pass off imperceptibly into panting or tachypnea, nor does it at its slowest rate grade into the slow, sighing rhythm. Although in the medullary preparation it has recognizable resemblances to normal breathing, it nevertheless differs in one essential characteristic, i. e., in a lack of uniform regularity in amplitude and in rate, giving the all-over picture of eupneic respiration at the medullary level an appearance of incomplete regulation, which reflects its extreme deprivation of modulating influence from higher centers and from afferent nerves (Fig. 2). Indeed, "medullary" breathing is invariably characterized by this "ataxic" type of eupneic respiration. It differs from eupnea in the more integrated preparation in another

direction, also, for breaths are abrupt and jet-like in their appearance and course and lack the element of restraint or breath holding which gives to normal respiration its smooth curve of inspiration and expiration. The total duration of the act of inspiration and expiration in the medullary animal is, in consequence, significantly shorter than it is at any more highly integrated stage.

At this level of integration section of the vagus nerves produces no essential change in the pattern of respiration itself (Fig. 2). The ataxic pattern of the typical medullary preparation is not slowed by vagotomy, and the only change ordinarily seen is a moderate increase in both rate and amplitude. Less frequently, the rate and depth of respiration may diminish somewhat, indicating that both excitatory and inhibitory influences do indeed exist in the afferent vagal supply, but that these are not of great moment in regulating the rate and depth of breathing at this level. The great increase in depth and the slowing of respiration, supposedly characteristic of deprivation of the medullary center of vagal influences, do not occur at this level, and one is forced to the conclusion that the limiting influence of the so-called Hering-Breuer reflex on the depth of each inspiratory effort is not particularly important, if, indeed, it takes place at all. Thus, as far as medullary respiration is concerned, the vagus can be denied both of the functions usually attributed to it; neither does it participate in the actual initiation of expiration by inhibition of inspiration, and in consequence have an essential role in the production of rhythmicity itself, nor does it have any preponderant or immediate role in the limitation of the depth of each inspiration. Rather, it can be presumed that the vagi do exert at this level an all-over inhibitory function, on both rate and depth, as well as an excitatory function, which is usually masked by the inhibition and which is only occasionally revealed by vagotomy. This is not to deny an important, but different, role to the vagi, as will be seen later; but this function is carried out at a supramedullary level and not within the medulla itself.

All-or-Nothing Respiration.—At the medullary level the all-or-nothing type of respiration is also present, often as a pattern of superimposed respiration appearing against the eupneic background at a much slower rate (Fig. 3*A*) and at other times as the sole visible rhythm, or nearly so (Fig. 3*B*, *C*). Most frequently its rhythm is not well maintained and is slow and irregular; but often as the condition of the animal deteriorates, its rhythm stabilizes and quickens, and usually the last breaths of the deteriorated animal will be of this type. At other times, and for long periods, animals in good condition will display this rhythm strongly in circumstances in which anoxia and deterioration do not appear to play a preponderant role, so that, while these factors obviously enhance this slower rhythm, they are by no means the sole factors, and it is inadvisable to employ the term of "gasping" respiration, which carries a connotation of air hunger.

At supramedullary levels this rhythm attains fuller expression and gains the drive which permits it to be the basis for periodic breathing. Once the pons, in whole, or even in its lower reaches, is added to the medullary respiratory system, certain changes take place in the pattern of breathing. First, the eupneic background regularizes in both rhythm and depth, and the "ataxia," which so strongly characterized it in the medullary preparation, disappears. Next, the all-or-nothing rhythm usually quickens; it invariably becomes more regularly spaced, and it exerts a profound but variable inhibitory influence on eupnea. Thus, the first few breaths after

a deep sigh may not appear at all, producing an obvious "silent period" in the respiratory record after each all-or-nothing breath. The first few eupneic breaths that then appear are likely to be reduced in amplitude, and recovery to full amplitude may take the entire cycle; and in these instances it may indeed be possible that a strongly marked, deep sighing rhythm may depress the entire background of eupnea; there never being time for the eupnea to recover fully from the inhibition following each deep breath.

This pattern is the prototype of respiratory periodicity, containing, as it does, the basic components of all related periodicities: (*a*) a slow rhythm, of variable rate, ranging from several per minute to one in several minutes, and (*b*) a mechanism for reciprocal inhibition of eupneic breathing, which can create gaps in the respiratory

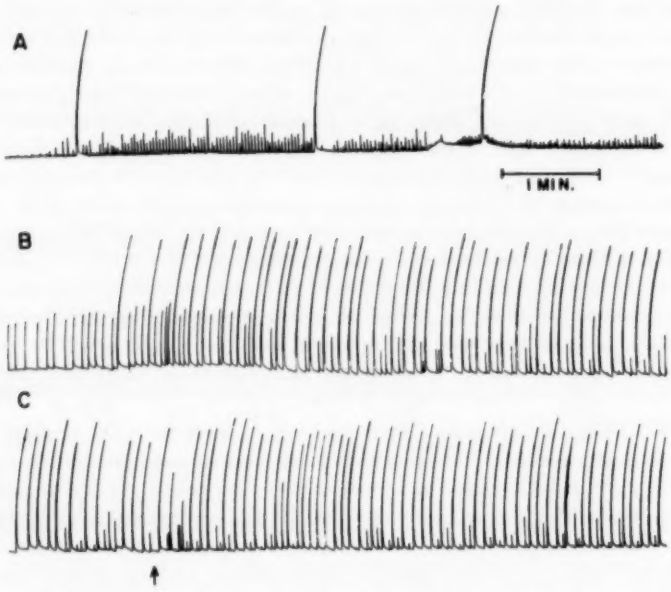

Fig. 3.—*A*, Dog 290-B: medullary transection, showing low-amplitude, ataxic eupnea, with all-or-nothing breaths at an irregular rhythm, followed by some inhibition of eupnea. *B* and *C*, Dog 298-B: continuous records of breathing in medullary preparation, showing spontaneous transition from eupneic breathing to fairly rapid all-or-nothing breaths. Eupnea diminishes and nearly, but not quite, completely disappears. In *C*, vagotomy (Arrow) does not essentially alter the pattern of breathing. Inspiration upward.

pattern. Thus, the normal, decerebrate animal, with its vagi intact, and presumably completely normal as far as circulation and gas exchange are concerned, exhibits the fundamental periodic rhythm and possesses the basic neural attributes for the development of other types of periodic breathing. The fundamentals of respiratory periodicity are therefore intrinsic.

It may be presumed that the accentuation of this slow rhythm in the decerebrate animal, in comparison with the medullary animal, derives from facilitatory impulses originating in the excitatory system of the reticular substance of the pons, descending to the medulla by multiple relays within the reticular mechanism. Further, it may

be presumed that this accentuation in the decerebrate animal is more pronounced than is normally seen in the intact animal and results from a differential between suppressor and excitatory mechanisms akin to that which produces decerebrate rigidity in the same animal. Thus, the cortex and upper brain stem may be thought of as sources of suppressor impulses which have been cut off in the decerebrate animal and which in the intact animal diminish, and even abolish, this slow rhythm from normal breathing.

The vagi must be regarded as another source for suppression of this rhythm, for when the vagi are sectioned, in part or completely, the slower, all-or-nothing rhythm becomes still more pronounced (Fig. 4*C*), while the inhibition of eupnea increases to such a degree that after complete section of both vagi in the classic midcollicular

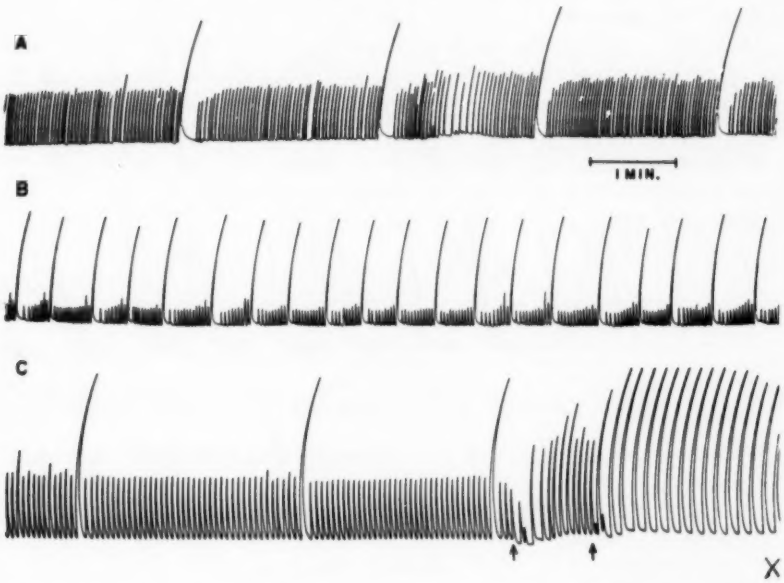

Fig. 4.—*A*, Dog 303-B: midcollicular decerebration; vagi intact. *B*, Dog 263-B: midcollicular decerebration; vagi intact. *C*, Dog 305-B: midcollicular decerebration; vagi cut during record (between Arrows). These figures illustrate the regularization of rhythm and rate of both eupneic and all-or-nothing breathing in the decerebrate animal, forming a characteristic double pattern. The variable inhibition or suppression of eupnea after each deep breath is well illustrated. In *C*, vagotomy substitutes an accelerated all-or-nothing rhythm for the prevagotomy pattern.

animal, eupnea is completely suppressed and the all-or-nothing rhythm becomes the sole respiratory expression. The effect of vagotomy is not, therefore, to remove inhibition of eupnea, as is the usual explanation of this change in respiratory pattern, but, rather, to increase the inhibition of eupnea through "release" of the all-or-nothing rhythm. This process is almost entirely centered in the brain stem above the medulla, for animals without the pons fail to show any significant change after vagotomy, as they equally fail to show the characteristic periodic pattern of the decerebrate animal.

The indispensable anatomical minimum for this phenomenon lies at the level of the lower part of the pons; whether the pons itself is simply a fortuitously convenient

landmark or whether it is in one way or another functionally significant is at present largely conjectural.

Unquestionably the three fundamental patterns of breathing, closely related as they are, yet clearly disparate in many neurophysiological details of origin and control, have a biological purposiveness in keeping with their semiseparate identities, which will undoubtedly become more apparent as more and more of the minutiae of their anatomical substratum and physiological operation are revealed. Nevertheless, some indications of functional values are already visible in outline, if not in detail, for it is noticeable that eupnea and the all-or-nothing rhythm form more or less reciprocating systems in which, within certain limits, factors suppressing the one system enhance the other. Here, then, is a mechanism for maintaining ventilation beyond the homeostatic limits of a single system. In the completely normal organism

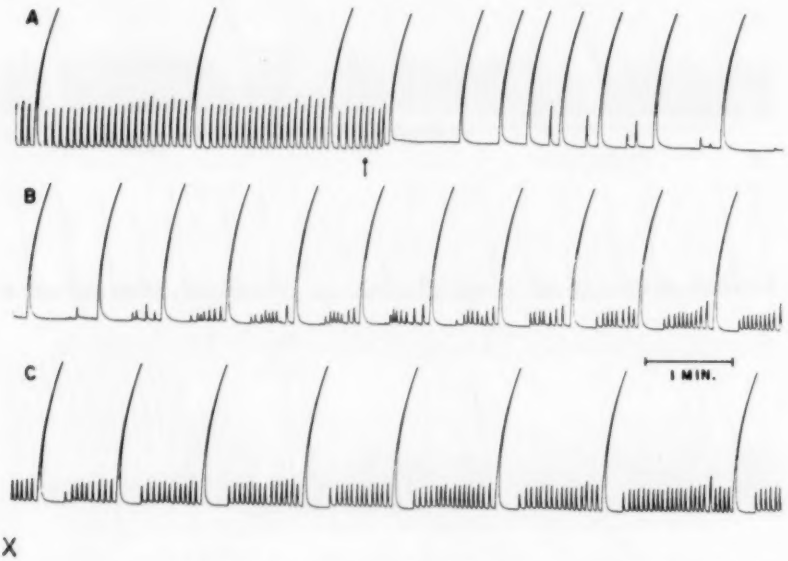

Fig. 5.—Dog 279-B: midcollicular decerebration with typical "decerebrate" respiration. In *A* (Arrow), the administration of 5 mg. of racemorphan quickens the all-or-nothing breathing and virtually eliminates eupnea. In *B* (continuous with *A*), there is progressive return of eupnea, with marked postsigh inhibition. In *C*, this feature is still retained, and eupnea has not yet reached the preracemorphan level. Note the increase in all-or-nothing breathing that substitutes for the failure of eupnea. Compare the almost identical, but irreversible, effects of vagotomy in *C* and Figure 16*A*.

the slower system is totally suppressed, while eupnea is most fully developed and integrated. With damage to the cortex, or its suppression by narcotics or sleep, the slow rhythm is released and becomes more and more pronounced the greater the narcosis or damage. In anoxia and air hunger the same phenomena occur, so that at levels of anoxia at which normal eupnea has completely failed an accelerated all-or-nothing breathing remains as the last observable act in the dying animal, occasioning its designation as "gasping respiration" by Lumsden.[10]

This serviceable reciprocation is strikingly illustrated by the administration of morphine or related compounds, such as racemorphan (Dromoran), to the normal

or decerebrate dog, where these agents act, as in other levels of transection, to suppress eupnea. However, in the same proportion as eupnea is depressed the all-or-nothing rhythm is accentuated, so that no matter what dose is given breathing is preserved (Fig. 5). It is therefore difficult to kill these animals with the drugs mentioned. In the medullary animal, on the contrary, this intensification of the all-or-nothing rhythm does not occur, and administration of morphine and racemorphan in very small doses can produce apnea.

III. INSPIRATORY BREATH HOLDING

Apneustic Breathing.—The pons makes another contribution to the ensemble of respiratory adjustment which plays its own part in determining the pattern of breathing, for within the brain stem at the level of the pons are systems which regulate the "posture," "tonus," or expiratory volume of the thorax, and which are associated with those systems regulating respiratory rhythm.

If the vagi are sectioned after classic midcollicular decerebration, only those changes occur which have already been described; eupnea is inhibited and replaced by an accelerated all-or-nothing rhythm. When, however, the transection is made within the limits of the pons itself, as is best illustrated following a midpontine section, not only does breathing become periodic, but, in addition, each period is marked

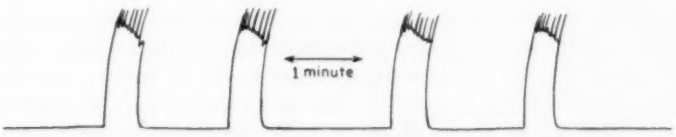

Fig. 6.—An example of apneustic breathing after midpontine transection and vagotomy, fairly typical in rate, duration, and completeness of inspiratory breath holding.

by a prolonged inspiratory spasm which entirely or largely occludes the respiratory movements of thorax and diaphragm (but not of the facial muscles), producing what is termed apneusis, or apnea in inspiration (Fig. 6). In time the apneustic intervals become shorter, and breathing is segmented into intervals of inspiratory breath holding and expiration. This is apneustic breathing. If the pons and upper part of the medulla are then removed, both the periodicity and the inspiratory breath holding vanish, and the ataxic breathing of the medullary preparation appears.

It has been postulated that the inspiratory breath holding of apneusis or apneustic breathing constitutes a sort of "decerebrate rigidity" of the respiratory system, and that this results from overactivity or, more exactly, from unopposed activity of a portion of the reticular excitatory system located at the level of the lower pons, and normally held in check by afferents to the suppressor system from the upper part of the pons and from the vagi, either of which alone can prevent inspiratory hypertonicity. When both moderating influences are gone, as occurs after vagotomy in the midpontine animal, the facilitatory system preponderates and inspiratory spasm intervenes, to be segmented, eventually, by the slow rhythm which has also been "released" by the same procedures.

The midpontine animal, showing, as it does, apneustic breathing after vagotomy and a maximum decerebrate rigidity, is also characterized by equally striking changes in the autonomic sphere. Sialorrhea, rhinorrhea, and, before the vagi are cut, brady-

cardia and hyperperistalsis point to a syndrome of parasympathetic preponderance, originating in an imbalance in the suprasegmental regulation of the autonomic sphere, akin to that which produces inspiratory and somatic spheres. This bradycardia is usually diminished with inspiratory effort and is progressively reestablished thereafter, so that the maximum of bradycardia is often reached just before the next breath is taken.

There are ample indications of the function of the apneustic mechanism in health and disease. It is, of course, recognized that the excursions of the chest which provide for tidal exchange of air take place against a background of inspiration; normally the tidal volume is approximately equidistant from full inspiration and maximum expiration. Thus, increase in depth of breathing can be provided as well by fuller expiration as by completer inspiration. Most phasic processes in the somatic sphere are similarly organized; walking, running, scratching, etc., are in reality phasic variations of a background of tonic skeletal muscular activity which maintains body posture and a temporary attitude and position appropriate to the phasic movement of the moment. Thus in the scratch reflex in the dog, elicited by stimulation of the shoulder, postural adjustment of the body as a whole releases the appropriate hindlimb from its responsibilities in standing, and a second series of tonic adjustments brings the foot to bear on the stimulated area and maintains it there, while more limited phasic variations in this posture provide the actual scratch.

Undoubtedly the inspiratory tonus of the thoracic musculature participates in much the same manner in the actual maintenance of posture, for indeed the muscles of inspiration are fundamentally extensor muscles, and repeated examples are seen of the close affinities between extension and inspiration and between expiration and flexion. In taking a full inspiration the back and neck are hyperextended, while full expiration can be accomplished only with the assistance of fairly generalized flexion. Yawning, sighing, and other acts involving deep inspiration are often accompanied by extensor movements in the body and limbs. There is often trembling in extensor muscles during inspiration in the normal dog, and this is more pronounced after midcollicular decerebration, where an augmentation in decerebrate rigidity, marked by hyperextension of the four limbs and opisthotonos, may accompany each inspiration and fade with each expiration. In the first instance, then, inspiratory tonus is part of the general postural apparatus of the body, and it is not surprising that it finds its suprasegmental regulation in the same area of the brain stem that regulates posture. While, to be sure, decerebrate rigidity may be found after transections that will not yield apneusis or inspiratory breath holding upon vagotomy, nevertheless, maximum decerebrate rigidity is attained at the midpontine level, which coincides with the level at which maximum inspiratory breath holding is achieved.

Numerous accounts point out that stimulation of afferent fibers in the vagus will inhibit skeletal muscular tone much as it will inhibit respiration; and, conversely, it has frequently been observed in the course of these experiments that when the vagi are sectioned to produce apneusis in an appropriately prepared animal, decerebrate rigidity markedly increases. This reinforces the view, expressed earlier, that the vagi contribute to the reticular substance supporting the suppressor system generally, and that the so-called "centers" that regulate respiration above the medullary level are not "centers" in the 19th century sense of isolated nuclear masses subserving specialized functions, but are semispecialized portions of a widespread reticular

system that provides a common denominator of integration, "infiltrating" the more specialized nuclear masses of the brain stem and mediating without doubt that harmonious cooperation of motor activity in somatic, autonomic, and respiratory spheres which is so apparent in almost every act of the animal organism, but which finds such inadequate expression in a physiological language that has grown from centuries of analytical studies.

But the level at which the expiratory position of the thorax is maintained is even more intimately related to respiratory function itself. Clinicians have long been aware of the increase in the resting volume of the chest during the dyspneic phase of Cheyne-Stokes respiration, and it is readily demonstrated that during states of anoxia this volume increases progressively. Gesell and Moyer [11] noted an increase in the circumference of the chest and abdomen of dogs during anoxemia, and Harris [12] found that when cats became anoxic the resting lung volume increased by a volume as much as three times the normal tidal volume.

This response has been considered by some to be a compensatory device, operating to mitigate the effects of oxygen lack through dilation of the alveolar spaces and widening of the lung capillaries, thus, presumably, permitting maximal utilization of the oxygen available. It is a reasonable assumption that the mechanism operates via the chemoceptors of the carotid body and the aortic arch, and Harris found, in partial confirmation, that the vagi were responsible for approximately two-thirds of the reaction. Section of the nerves to the carotid body had little influence on the reaction in Harris' experience, but, on the contrary, in many of the experiments which form the experience of this report, procainization, or denervation of the carotid sinus area, or section of the glossopharyngeal nerves greatly reduced the degree of apneusis. Carbon dioxide did not by itself increase resting thoracic volume when added to the respiratory mixture in excess, although it sensitized the animal to low oxygen. Perhaps this mechanism was involved in the increase in apneusis reported by Stella [13] when CO_2 tension was increased.

However the mechanism may be involved in the physiological response to anoxia, it appears certainly involved in a variety of pathological responses. Haldane and Priestley [14] have called attention to the progressive shallowness of breaths attendant upon anoxia, and Harris has pointed out that in effect the growing inspiratory hypertonus encroaches more and more on tidal volume as the upper reaches of the vital capacity are approached, and that the gap between expiratory position from which each new breath must start and maximum inspiration, which forms its upper limit, is progressively narrowed. If, then, increase in resting thoracic volume is a compensatory process with lower degrees of anoxia, it becomes anticompensatory at the more extreme limits and constitutes a definite hazard to respiration. Thus it happens that persistent states of inspiratory hypertonus seen in emphysema and asthma develop, and thus it comes about that the very state of increased lung volume seen in these conditions initiates a vicious cycle of increasing anoxemia and increasing thoracic volume. In consequence, procedures designed to lessen lung expansion, as by pneumoperitoneum, may actually increase tidal volume.

Apneustic Breathing in Man.—During a demonstration of apneustic breathing in the cat given in this laboratory, a physician present was struck with the resemblance between it and a respiratory syndrome which his brother had shown after an attack of epidemic encephalitis in 1920. Periodically, the patient would fall upon his bed in an exaggerated extensor posture, inspire fully, and hold his breath for

some time. Then he would double up, exhale, and take a few normal breaths, only to repeat the act. After a year and a half, the syndrome disappeared with the onset of hemiplegia.

Similar reports have been collected in the literature of the early 1920's, in which the apneustic syndrome is described, though at times the connection with encephalitis has not been realized. One of the most graphic is the following description by Peck.[15]

Case 1.—W. F., a boy of 15 years, was admitted to the hospital May 27, 1921, referred from the outpatient department, where he had been taken on account of stereotyped stretching movements, over which there was apparently no control. These compulsive acts began in March, two months previously, and consisted of a definite cycle of activity. First the hands were lifted above the head in the manner of normal stretching; after this the head was thrown back almost at right angles, the chest and abdomen thrust forward, and the breath held in deep inspiration; while one or both hands were stretched down at the side and held rigidly with fingers separated in an awkward manner. During the latter part of the exercise, the face was expressionless, eyes wide open with unseeing stare directed upward, and the whole body strained and tense. The period of apnea lasted about five seconds and was followed by sudden relaxation and assumption of normal posture, though breathing was labored for a few moments as a result of exhausting effort. In the state of apnea the patient would not respond to command and appeared wholly oblivious to his surroundings. As soon as it was over, he would usually pick up the thread of a conversation or answer questions in a way to show there was no real clouding.

Parker,[16] Hughlings Jackson and Barnes,[17] Speirs,[18] Stern,[19] and others have described similar cases in which the association of apneusis with postures recalling decerebrate rigidity is uniformly observed. In addition, the presence of sialorrhea, vomiting, or bradycardia is often mentioned. There is thus an almost perfect accord between the syndrome of apneustic breathing in man and that in experimental animals.

IV. BIOT'S BREATHING

In the strictest sense, apneustic breathing is solely an alternation between periods of full inspiratory breath holding and complete exhalation, but as it is recorded it is rarely free from a phasic component, which indicates plainly that phasic breathing is continuing however much it is submerged or "occluded" by the inspiratory spasm. In these circumstances phasic breaths form a "fringe" on an apneustic base line, which varies reciprocally with the apneustic element. Thus, at the opposite extreme of apneustic breathing are segmented clusters of breaths separated by periods of apnea, which constitute Biot's ‡ breathing, and between these two extremes are all degrees of transition in which only the degree of respiratory breath holding can serve as the criterion in designating it as Biot's or apneustic breathing; the periodicity is common to both apneustic and Biot's breathing, it is the slow periodicity of the all-or-nothing rhythm.

Even in experiments in which the inspiratory effort in apneusis is total and no phasic variations occur in the thorax during apneusis, rhythmic breathing movements may often be seen to continue in the facial musculature, indicating the persistence of a central rhythmic activity despite the apneustic overlay. Usually this breathing is interrupted during the period of apnea, producing a periodic respiratory rhythm exactly like that seen in the same musculature during Biot's breathing. Because of the nonparticipation of the facial musculature in respiratory spasm, Biot's breathing alone is seen here.

‡ References 20 and 21.

It has already been emphasized, and from the above it is readily apparent, that the slow rhythm of breathing which lies at the basis of respiratory periodicity and the inspiratory breath holding which form the characteristic features of apneustic breathing are separate and separable components, although, to be certain, they both are mediated within the reticular facilitatory system. Although in the progress of deterioration of a preparation they may be extremely sharply differentiated, it is less easy to accomplish such a division by means of a transverse section. There are, however, a number of other circumstances in which the relationship of apneustic to Biot's breathing may be demonstrated and which have, in addition, direct physiological significance; these can now be discussed.

A. Conversion of Biot's Breathing to Apneustic Breathing by Vagotomy.—Not infrequently it occurs that the midpontine decerebrate animal will spontaneously show Biot's breathing, owing undoubtedly to brain stem damage from anoxia, hemorrhage, etc. Figure *7* is an example of such an experiment, in which segmented sequences of breathing occurred at intervals of approximately one minute. Only a very slight element of inspiratory breath holding is seen in each group of breaths, so that this can be considered as almost "pure" Biot's breathing. The vagi were then sectioned, without change in the fundamental periodicity, but a marked degree of inspiratory breath holding now appeared, producing a typical record of apneustic

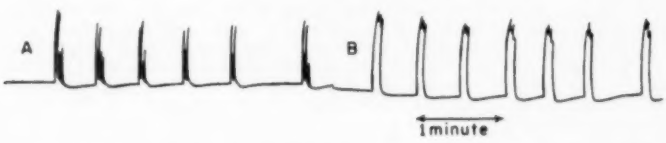

Fig. 7.—Dog 243-B: midpontine decerebration, with spontaneous development of Biot's breathing (*A*). Vagotomy then produced apneustic breathing, in which the periodicity of Biot's pattern is preserved, with the addition of breath holding during the whole period of breathing. Phasic breathing is not completely submerged by the strong inspiratory hypertonus.

breathing. Despite the extreme inspiratory position, there is nevertheless visible a small "fringe" of phasic breaths, which makes it clear that all that has happened has been the increase in the inspiratory position of the chest, without any essential change in the fundamental periodicity upon which it is in reality superimposed. As has been emphasized before, the inspiratory spasm simply "occludes" the respiratory movements.

B. Conversion of Apneustic to Biot's Breathing by Mephenesin.—Revelation of the role the facilitatory and suppressor components of the reticular systems play in production of pathological states of muscular spasm has stimulated search for drugs which act with some measure of specificity on the multineurone relays of which the reticulum is constituted. Mephenesin is one of the family of compounds that appear to depress this system preferentially, and it has found employment in a number of clinical states of facilitation-suppression imbalance. In the decerebrate animal it abolishes decerebrate rigidity. In consequence, it should be expected to abolish equally the respiratory signs of the same imbalance in the suppressor-facilitatory mechanisms. This, in fact, it does and, when given to an animal breathing apneustically, will abolish apneustic breathing and establish typical medullary breathing. In this process Biot's breathing often appears as the inspiratory breath holding is

eliminated, while the underlying periodicity persists. Figures 8 and 9 illustrate this process. In Figure 8 typical apneustic breathing was produced by midpontine transection and vagotomy. The periods of breath holding, though short, indicate nearly full inspiration by a minimum of the phasic component. One-fourth gram of mephenesin in solution was then given intravenously, with immediate loss of the component of inspiratory breath holding along with some slowing of the cycle and with concomitant increase in the phase of breathing. Thereafter there was rapid restoration of the rate and inspiratory breath holding.

In Figure 9 the apneustic breathing appearing after midpontine transection and bilateral vagotomy was somewhat less extreme, and, as can be seen, there is a greater element of phasic respiration, especially noticeable in the presence of two deep phasic breaths after the breath-holding phase, almost exactly the pattern described in the

Fig. 8.—Dog 54-B: midpontine transection followed within 15 minutes by bilateral vagotomy, producing apneustic breathing. In two earlier trials this pattern had been abolished and had then returned after appropriate doses of mephenesin. After the fourth breath 250 mg. of mephenesin in solution was injected, with immediate disappearance of the respiratory breath holding and conversion of apneustic to Biot's breathing. After approximately 15 cycles, Biot's breathing was reconverted to apneustic breathing by the reappearance of inspiratory breath holding. It is noticeable that the first three cycles after the mephenesin was given have definite affinities with Cheyne-Stokes respiration, showing both a slight waxing and waning of amplitude and a small element of tonus change during the respiratory phase. Inspiration downward. Time in 10-second intervals.

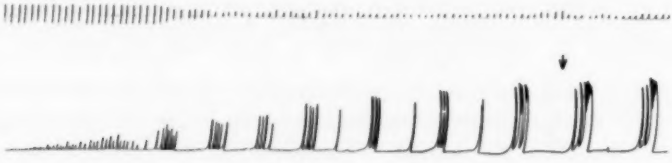

Fig. 9.—Dog 76-B: midpontine section followed within 20 minutes by bilateral vagotomy, producing apneustic breathing with a greater admixture of phasic breathing than in Figure 11. A constant intravenous drip of mephenesin in solution being started at the Arrow, inspiratory breath holding was quickly abolished and Biot's breathing produced. In the final stages before respiratory arrest periodicity itself disappeared. Inspiration downward; time in 10-second intervals.

clinical case cited above. Mephenesin solution (0.42 gm. in all) was injected by a constant drip until respiratory arrest. The progressive loss of the component of inspiratory breath holding is clearly recognizable, while the periodicity remains as segment breathing in the characteristic Biot's pattern. It is noticeable also, and it will be discussed in greater detail later, that as injection continued, periodicity was lost, and the terminal breaths, although reduced in amplitude by the drug, were nonperiodic.

C. Morphine and Racemorphan.—The foregoing illustrations of the action of mephenesin leave little doubt that periodic breathing represents fundamentally the segmentation of the basic rhythm of breathing as generated in the medulla by a

slower rhythm, and that upon this periodicity a varying amount of inspiratory breath holding is superimposed, to give at one extreme apneustic breathing, and at the other Biot's breathing. It is evident also that both the inspiratory breath holding and the periodic segmentation of breathing are manifestations of the activity of the reticular facilitatory system, but that the two are nevertheless separable.

Further illustration of the functional relationship between Biot's and apneustic breathing is afforded by studies of the respiratory action of morphine and a related synthetic material racemorphan. These drugs are of interest because of the recognition within recent years that they also depress multineurone arc responses (Wikler [22]). Figure 10 exemplifies this feature of the activity of morphine in a dog breathing with a marked apneustic rhythm. Forty milligrams of morphine sulfate was given intravenously, producing complete loss of apneusis and an irregular rhythm of deep breaths. These breaths then were segmented into periods typical of Biot's breathing, except that there was some regular variation in amplitude of the breaths in each cluster and a small element of inspiratory tone.

Racemorphan has been proved even more effective than morphine in this pharmacological differentiation, possibly because of the less marked accompaniment of

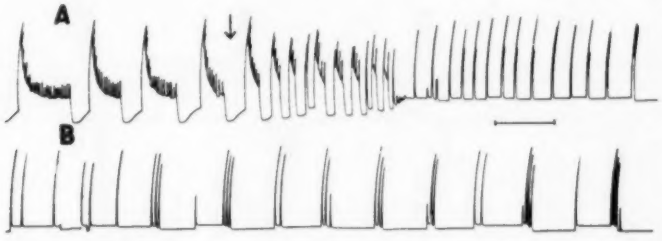

Fig.10.—Dog 257-B: midpontine transection and bilateral vagotomy with development of apneustic breathing, with a definite phasic component. Forty milligrams of morphine sulfate was injected intravenously (Arrow), with prompt diminution in duration of apneustic breaths and, within three minutes, practically complete disappearance of the apneustic element and establishment of an irregular deep rhythm. Soon, however, a definite periodicity was established of the usual Biot's character (*B*). Later this was modified by development of a small element of inspiratory breath holding and signs of incrementing and decrementing amplitude, bearing affinities with Cheyne-Stokes respiration. Time mark between *A* and *B* equals one minute.

cardiovascular changes. Figure 11 records the respiration of an animal in which Biot's breathing developed spontaneously after a midpontine transection. Section of the left vagus had no effect on the pattern of breathing, but when the right vagus was severed there appeared in the next cluster of breaths a strong element of inspiratory spasm, together with a slight increase in the duration of the respiratory phase. There was, however, no essential change in the periodicity. Two successive doses of 5 mg. of racemorphan progressively reduced and a final dose of 10 mg. of racemorphan finally abolished the apneustic element, without significant change in the periodicity of breathing.

Figure 12 affords a more striking example in a midcollicular decerebrate animal, in which after vagotomy an initial dose of racemorphan produced apneustic breathing so complete that phasic respiration barely existed. Ten milligrams of racemorphan then completely abolished the apneustic element, with maintenance of the basic periodicity in Biot's breathing.

D. Deterioration and Anoxia.—Not infrequently the differentiation achieved above by the appropriate drugs has appeared as part of the pattern of deterioration in a preparation, whether by anoxia, hemorrhage, or other factors. Figure 13*A* and *B* illustrates interesting intermediate stages in this process in two experiments, in which the apneustic component was greatest at the onset of each phase of breathing and fell away progressively as breathing continued until no apneustic element

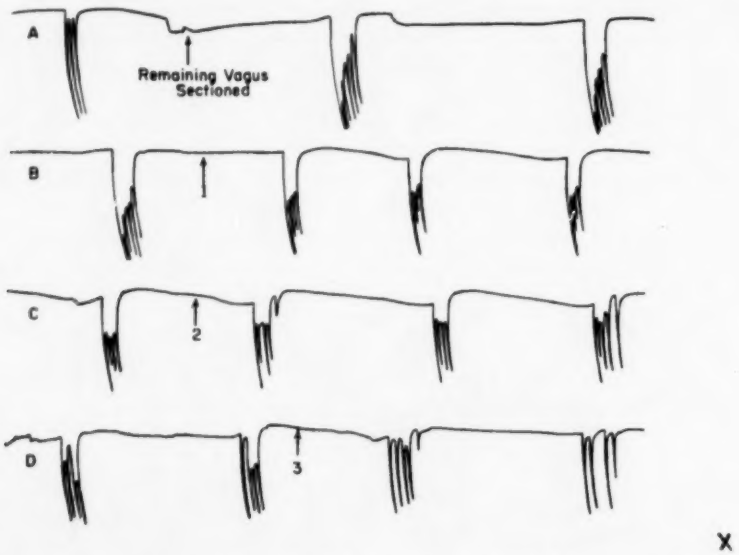

Fig. 11.—Dog 202-B: midpontine section, with development of Biot's breathing at a slow rate, as seen in the first complex in *A*. Section of the left vagus without effect, but on section of the right vagus (Arrow) a strong phasic apneustic component appeared in the next respiratory complex. This apneustic element was reduced by two successive doses of 5 mg. of racemorphan intravenously in *B* and *C* (Arrow *1* and *2*). It was finally abolished in *D* by a final dose of 10 mg. of racemorphan (Arrow *3*). The animal survived for 70 minutes thereafter, with a virtually unchanged pattern of breathing.

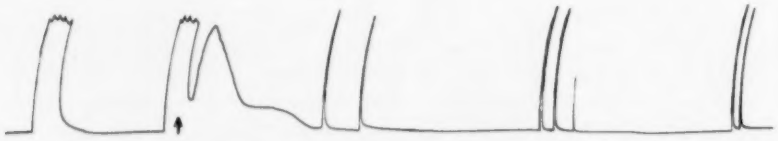

Fig. 12.—Dog 286-B: midcollicular decerebration and vagotomy, with characteristic apneustic breathing. Ten milligrams of racemorphan (Arrow) abolished all traces of apneusis and established Biot's breathing.

remained. In both experiments all traces of apneusis disappeared later, leaving pure Biot's breathing.

E. Anatomical Substratum of Biot's Breathing.—Figure 14 is from an animal with a transection at the level of the trapezoid body, in which on vagotomy periodic breathing appeared, fundamentally of Biot's character, superimposed upon a postural shift in thorax and limbs at an associated rhythm without the sharp features of

apneustic breathing. Here is one of the not infrequent occasions in which the section was fortunately made at a level that largely differentiated between the apneustic element and the periodic component. The pattern indicates, as does other evidence, that the component of apneusis or inspiratory breath holding is largely an element of origin within the supramedullary regions of the brain stem, being almost invariably absent in medullary preparations, as it is equally present when the brain stem at the

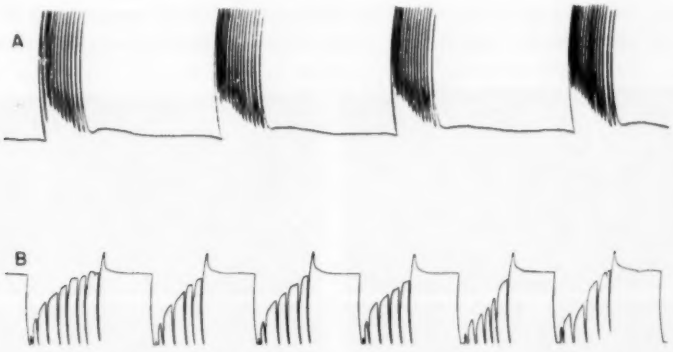

Fig. 13.—*A*, dog 113-B; *B*, dog 92-B: Two illustrations of transitional stages between apneustic and Biot's breathing in which there is a large element of inspiratory breath holding at the beginning of each respiratory cycle, followed by a gradual decline thereafter until at the end of the respiratory phase there is no apneustic element. Inspiration up in *A*, down in *B*.

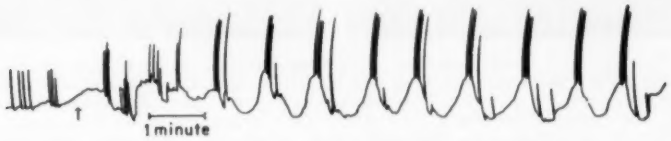

Fig. 14.—Dog 33-B: transection at the level of the trapezoid bodies, followed by vagotomy (arrow) with appearance of Biot's breathing superimposed upon generalized phasic postural movement, including increase in inspiratory position. The pattern differs from true apneustic breathing in its lack of abrupt onset and termination.

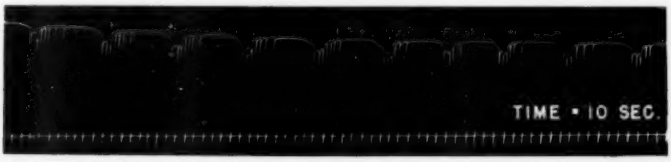

Fig. 15.—Cat 25-S: After midpontine decerebration vagotomy produced typical apneusis, followed by apneustic breathing. Medullary transection then abolished the apneustic breathing and restored a more normal type of breathing. Approximately half an hour later phasic bodily movements appeared, accompanied by respiratory segmentation, and these became more regular and persisted for the last half-hour of survival.

levels of the lower portion of the pons is included. The record indicates equally that Biot's breathing does not require the presence of these supramedullary centers for its appearance. Figure 15 is the record of a cat in which appropriate midpontine transection and vagotomy produced apneusis and apneustic breathing, which was then abolished by a high medullary transection and medullary breathing then established.

After approximately half an hour phasic postural movements which had respiratory counterparts began and partly segmented the breathing. Later these were more closely associated in fairly typical Biot's breathing, with a small postural element. It may be of significance in discussing the origin of this periodicity to note that for some time after the animal died the rhythmic postural changes persisted without any respiratory component. These same phenomena have been observed in animals with transections below the respiratory center; these animals were thereafter maintained alive with artificial respiration and showed periodic bodily movements at the frequency of the respiratory periodicity which they exhibited before this was abolished

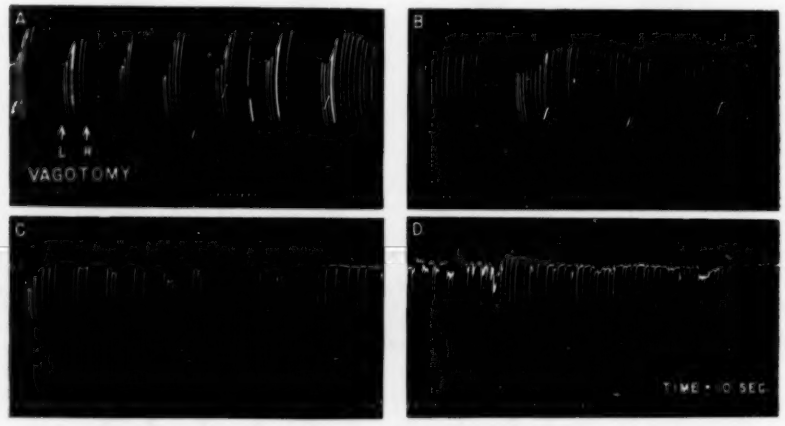

Fig. 16.—Dog 20-B: high medullary transection followed by Biot's breathing, unaffected by vagotomy (*A*). During the next hour and one-half the periodicity varied widely in rate (*B* and *C*). Finally (*D*), the periodicity was lost completely, and typical ataxic medullary breathing remained. The irregular periodicity (*C*) illustrates a transition between the more perfectly regular type (*A*) and nonperiodic medullary breathing (*D*) and corresponds more exactly with the classic description of Biot. Inspiration downward.

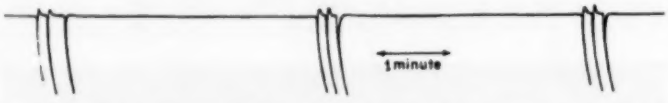

Fig. 17.—Dog 225-B: After a high pontine transection both vagi were sectioned, with the production of Biot's breathing at a slow rate, which persisted after a further transection at the upper border of the medulla. Thereafter, despite a variety of drugs, such as racemorphan and amphetamine sulfate, this pattern was maintained until death, eight hours later. This figure was taken from the record six hours after onset of Biot's breathing, and two hours before death, and is typical of the entire record, with intervals of approximately four minutes between each series of breaths. This experiment illustrates clearly that the neurological substratum for Biot's breathing is found in the medulla. The periodic character of this breathing was lost only in the last 10 minutes of survival. Inspiration downward.

by the low medullary transection. Figure 16 is another illustration of the fact that the confines of the medulla provide an adequate substratum for the exhibition of Biot's breathing, but is a more typical example in that the periodicity disappeared as the experiment progressed, and the last pattern to persist was nonperiodic medullary breathing. A high medullary transection was followed immediately by the appearance of Biot's breathing, which was not affected by vagotomy (*A*).

During the next hour and a half of survival the periodicity changed, as seen in *B* and *C*, but still was accompanied by the postural changes seen in *A*. During the last 30 minutes of survival the periodicity disappeared (*D*), leaving typical medullary breathing. Figure 17 is an extreme example of the same phenomenon associated with a high medullary transection in a dog which showed Biot's breathing for eight hours. In the last 10 minutes of survival, however, the periodic character of the breathing was lost, and regular breaths of low amplitude formed the terminal pattern.

This has also happened when morphine, racemorphan, or mephenesin was given while Biot's breathing was present. Figure 18 illustrates this phenomenon in a vagotomized midcollicular animal, in which Biot's breathing was produced by an initial dose of 5 mg. of racemorphan, and in which a later dose of 15 mg. of racemorphan abolished the periodic character of breathing and established a medullary type of breathing, which persisted for the remainder of the survival period. Figure 19

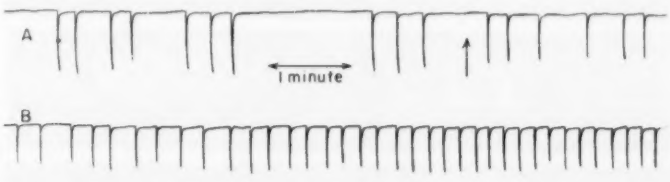

Fig. 18.—Dog 169-B: midcollicular decerebration with decerebration respiration. After bilateral vagotomy there was established a slow, sighing respiration, with a short apneustic element. A dose of 5 mg. of racemorphan abolished this apneustic element and instituted a slow Biot's rhythm (*A*). A further dose of 15 mg. of racemorphan then abolished this periodicity and restored nonperiodic breathing of the medullary type (*B*, continuous with *A*), which persisted throughout the subsequent hours of survival. Inspiration down.

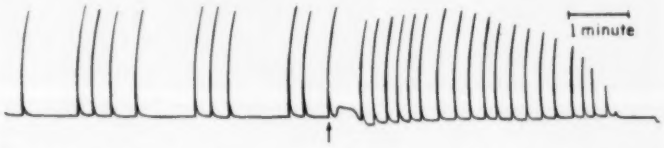

Fig. 19.—Dog 250-B: medullary transection and vagotomy. After administration of 30 mg. of morphine sulfate Biot's breathing was established, as seen in the first part of the record. Forty milligrams of morphine was then given (Arrow) with prompt regularization of rhythm. The pulse disappeared and the heart beat faded; concomitantly the amplitude of the respiration diminished, and the animal died.

shows the disappearance of periodicity when a fatal dose of morphine was given to an animal with a medullary transection and bilateral vagotomy after a first dose had established Biot's breathing. This is even more clearly demonstrated in Figure 20, the record of an animal that developed Biot's breathing after a high medullary transection and vagotomy; a minor element of inspiratory breath holding is apparent in the first cycles of *A*. A continuous drip of mephenesin was started at the beginning of the record, and it can be seen that this apneustic element was first to disappear. By the end of *C* the periodicity had practically disappeared, and the mephenesin was discontinued, whereupon throughout *D* the breathing was again segmented into periods. Mephenesin was again given in *E* and again the periodicity was abolished and ataxic medullary breathing reappeared. Thus the impression is gained that while the periodicity of Biot's breathing can indeed develop within the medulla itself, it

represents in almost all circumstances a physiologically more advanced level of integration of the respiratory pattern than does simple nonperiodic medullary breathing. In this sense it follows the pattern of the slow all-or-nothing rhythm which seems to provide its basic segmentation, for this type of breathing also develops in the isolated medulla but equally attains its full expression only after supramedullary facilitation.

In keeping with this view, gained from the foregoing experiments in which drugs, such as mephenesin and racemorphan, abolished the periodicity of Biot's breathing and established a nonperiodic breathing characteristic of the simplest medullary

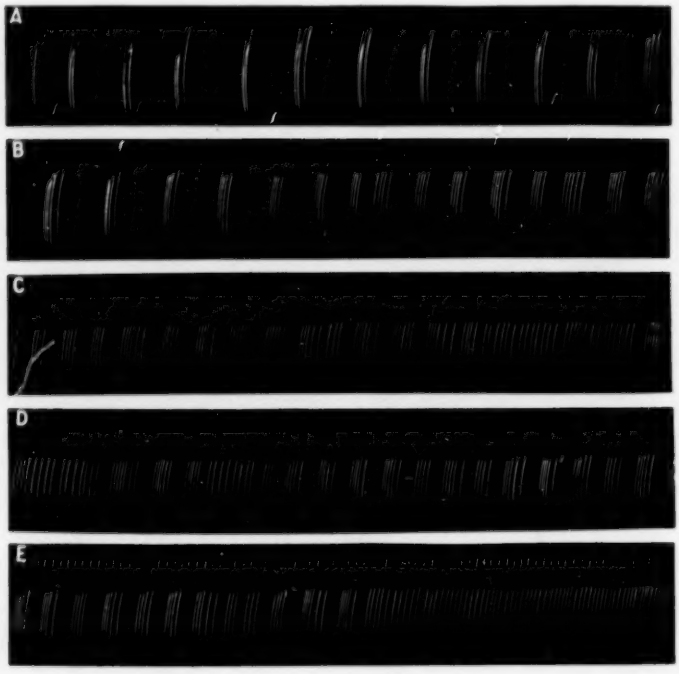

Fig. 20.—A continuous record of an experiment (dog), showing Biot's breathing following high medullary transection, in which intravenous drip of mephenesin produced a gradual change in the type of breathing until, at the end of the record (*C*), typical medullary breathing remained. Administration of the drug was then stopped, and during *D* periodic breathing reappeared, to be abolished again by a further dose of mephenesin in *E*. This experiment supports the concept that the rhythm of Biot's breathing is "superimposed" upon the fundamental, nonsegmented, medullary respiration, which is more resistant to the drug.

preparation, are the results of further transections of the neuraxis in those preparations exhibiting Biot's breathing. Here, with few exceptions, paralleling those seen also with drugs, it was usually possible to convert Biot's breathing to nonperiodic medullary breathing by a further transection lower in the medulla.

In the experiment illustrated in Figure 21 the transection was made in the lower part of the pons, with the result that on vagotomy periodic breathing with almost no apneustic component made its appearance (*A*). This was then abolished by a

transection within the medulla, unmasking typical nonperiodic medullary breathing (*B*). This breathing persisted, counting a period of apnea produced by racemorphan, for 3 hours 40 minutes, and no traces of periodicity reappeared.

The long periods of persistence of this ataxic nonperiodic breathing, appropriate to the level of transection, and the similar behavior after administration of drugs, in which a stimulating factor cannot be invoked strengthen the view that the periodicity of Biot's breathing in most instances is "superimposed" upon a basic propen-

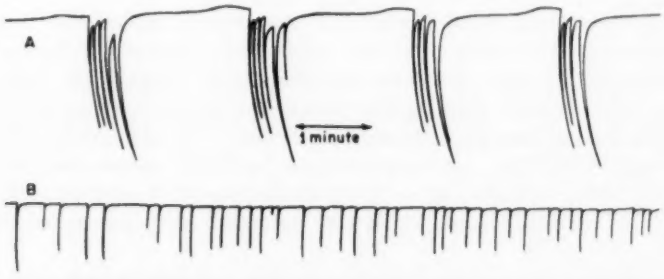

Fig. 21.—Dog 149-B: lower pontine transection, with typical Biot's breathing after vagotomy (*A*). A further transection in the medulla abolished this breathing and restored ataxic medullary breathing (*B*), which withstood a period of apnea reduced by racemorphan and was completely nonperiodic for the full survival period of 3 hours 40 minutes. Inspiration down.

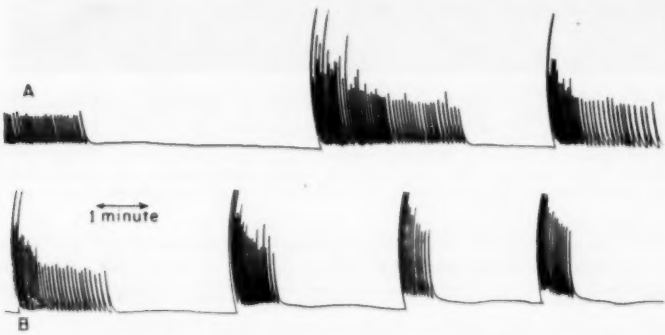

Fig. 22.—Dog 113-B: After midcollicular transection an appropriate pattern of decerebrate breathing was exhibited. It was then noticed that the animal was extremely sensitive to irritation of its trachea by the oxygen tube, each insertion serving to elicit a marked period of apnea. After this was done several times in succession, it was noticed that the periods of apnea returned spontaneously, producing Biot's breathing (with some admixture of apneusis at times), which persisted until the experiment was terminated, over an hour later. In *A* is seen the last period of reflex apnea, lasting four minutes; thereafter, in *A* and B the apneic periods are spontaneous.

sity of the respiratory center by some sort of first-level integration "above" the respiratory center itself, probably through facilitation of the inherent tendency toward the slow respiratory rhythm found in the medulla itself, while the disappearance of Biot's breathing results from the chemical or mechanical inactivation of these areas.

F. Periods of Apnea and Precipitation of Biot's Breathing.—Two observations bear on the problem of initiation of the rhythm of Biot's breathing. Figure 22 is

taken from the record of a preparation following midcollicular transection and the development of an appropriate decerebrate respiratory pattern. It was noticed that insertion into the trachea of the rubber catheter carrying oxygen produced marked inhibition of respiration. This was repeated several times, with the same results, and the first apneic interval in *A* is the last of those reflexly produced. Thereafter breathing became spontaneously cyclic and remained so until the experiment was terminated, over an hour later.

In Figure 23 the initial period of arrest was evoked in a cat by the intravenous injection of epinephrine, which produces its characteristic inhibition of respiration, at least in part, by some direct effect upon the central respiratory mechanism within the medulla itself. In the experiment illustrated, and in a significant proportion of all similar experiments, a single apneic dose of epinephrine is followed by further cycling of apnea and breathing. In the case of Figure 23 the Biot's breathing thus evoked continued until the experiment was terminated, 30 minutes later. In several experiments the administration of racemorphan in the medullary animal also produced short periods of apnea, which were then followed by periodic breathing.

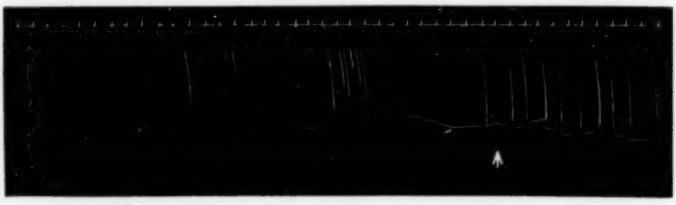

Fig. 23.—Cat 44-S: Transection was made between the trapezoid bodies and the medulla; the vagi and glossopharyngeal nerves were sectioned. Characteristic medullary breathing appeared and was maintained unchanged for a stabilization period of 40 minutes, when 0.25 cc. of 1:1,000 epinephrine was given (Arrow), producing promptly an appropriate arrest of respiration, lasting somewhat more than a minute. The subsequently resumed respiration was again terminated by a period of apnea, and so on, establishing a pattern of Biot's breathing, which persisted for 30 minutes.

These experiments imply that the apneic pauses in Biot's breathing bear close relationship to cessation of breathing in reflex apnea and in epinephrine apnea, suggesting perhaps that they have a common cause in a depression of excitability in the medulla, akin to central inhibition, anelectrotonus, or neurohumoral depression. It suggests also that the period of breathing that then follows, representing the release of the centers involved from this inhibitory bias, contributes in some way to the subsequent depressed state, somewhat in the manner of the alternating electrotonic potentials described by Lorente de Nó.[23]

That such slow changes of excitability may exist, even at a subthreshold state, is demonstrated without question in Figure 24, which portrays the breathing of a dog which went into apnea after classical midcollicular transection. Respiration was supported by oxygen and the animal was stimulated reflexly by rhythmic electrical shock to a paw. Each stimulus elicited a single reflex breath. It is noticeable that at regular intervals the response to the stimulus was greater than usual, and a deep, full all-or-nothing breath took place. The pattern of reflex respiration resembled exactly what would be expected as a pattern of breathing in the decerebrate animal,

the characteristic double rhythm of eupneic and all-or-nothing breaths. Indeed, when spontaneous breathing returned, an identical pattern was exhibited (*B* and *C*). Thus, even an apneic center, incapable of generating spontaneous breaths of any

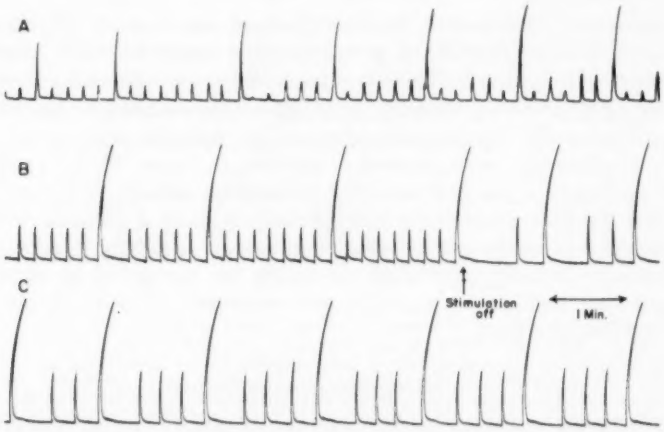

Fig 24.—Dog 334-B: A classic midcollicular transection was made under ether narcosis, and immediately thereafter the animal ceased breathing. Artificial respiration was instituted by cycled oxygen, until it was noticed that reflex breathing occurred in response to stimulation of the paw. Electrodes were then placed on the paw, and it was stimulated by rhythmic single shocks at a rate of approximately five per minute. A demand valve was substituted for the cycling device. In *A*, *B*, and *C*, which are continuous, is seen the evolution of autorhythmicity in this animal. In *A* there is a single small response to each stimulus, but at fairly regular intervals a much larger breath is taken. There is some tendency for the breaths immediately following these to be reduced in size. There is progressive improvement in the size of the responses of both types throughout *A*, and in *B* spontaneous breathing starts. It is clear that the stimulated breaths reproduce the pattern of spontaneous breathing except only in the rate of the eupneic breaths.

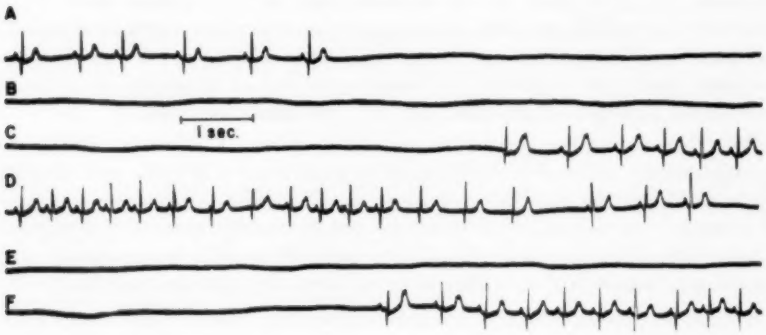

Fig. 25.—Dog 352-B: midpontine transection, without the decerebrate rigidity to be expected after a transection at this level and without the usual decerebrate pattern of breathing, but, instead with irregular Biot's breathing and variable periods of apnea and breathing. Cardiac arrest throughout each period of apnea. In this figure two typical cycles are shown.

kind, must be undergoing rhythmic changes in excitability that will later be expressed in a fundamental type of periodicity. The cycling mechanism is therefore not primarily dependent upon discharge, however much it may be altered by development of

propagated impulses. A parallel is seen in the observation that cycling mechanisms in simple nerve fiber preparations may preexist as cycled changes in threshold and potential at a subliminal level before they increase in amplitude and serve to trigger periodic discharges.

G. Autonomic Systems.—It has been pointed out that the supramedullary preparation exhibits a syndrome of parasympathetic preponderance in a wide spectrum of autonomic regulation. These changes have persisted in many of the animals which have exhibited Biot's breathing, although no special attention has been given to them. Occasionally, however, they have been so extremely accentuated that they could not be neglected. Such an event is recorded in Figure 25, which shows the electrocardiogram of a dog that exhibited an irregular periodicity of the true Biot pattern after transection within the pons, probably because of ischemia of the brain stem while the vagi were intact. During the periods of breathing there was unmistakable evidence of some vagal tone, but during the periods of apnea there was sudden and total inhibition of the heart, with resumption of beat only after a new cycle of breathing had begun.

V. CHEYNE-STOKES RESPIRATION

In the foregoing sections, a family of respiratory periodicities has been portrayed, and their relationship one to another has been traced. They have in common an inherent slow periodicity within the nervous system, possibly a physiological survivor of the swimming and other locomotor rhythms of simple forms, retaining physiological value as an added respiratory mechanism more resistant than eupneic breathing to adverse environmental conditions. Upon this substratum have been superimposed two variable components, one of inspiratory breath holding, finding its most complete expression in apneustic breathing, and the other a variable inhibition of eupneic breathing by the slow rhythm, which has been seen best in the "decerebrate" breathing, with its postsigh inhibitions, and in the cyclic variations in the amplitude of eupnea. The first factor is truly superimposed and is separable from the slow periodicity; the second, probably, is intrinsically an expression of the slow periodicity itself, associated with reciprocal inhibition in other spheres and bound up with the observable functional reciprocity in these two orders of breathing; it is therefore a part of the slow periodicity itself and not a separate component.

With these ingredients it is understandable how Cheyne-Stokes respiration might be compounded. The slow periodicity, waxing and waning as some such slow swing of potential might be expected to behave, would produce a corresponding waxing and waning of the amplitude of breathing and, eventually, periods of actual apnea, while the apneustic component would contribute the increase in expiratory position of the thorax, which reaches its height at the acme of respiratory amplitude.

It must be emphasized, however, that despite the reasonableness of this assumption Cheyne-Stokes respiration has not often appeared in the course of the experiments reported here, suggesting that full control of the various operating factors has not yet been achieved. While this cannot be denied, it seems logical also to invoke a species difference, for, indeed, Biot's breathing of the type seen so frequently in the dog and cat is less often seen in man.

However this may be, a not inconsiderable number of experiments point so strongly toward Cheyne-Stokes respiration that it seems obvious that this kind of

periodic breathing is also a member of the respiratory family described here. Figure 26 can serve as an example of a number of experiments in which the typical pattern of Biot's breathing is altered, and the individual breaths of each group are arranged in ascending, or, more rarely, a descending, order of magnitude. Additionally, in the last group it can be seen that small, almost imperceptible breaths are recognizable throughout the greater part of the apneic interval, as is not infrequently observed in Cheyne-Stokes respiration.

In Figure 27 a more complete evolution is observable. *A* records the apneustic breathing emerging after an appropriate midpontine transection and vagotomy, and in

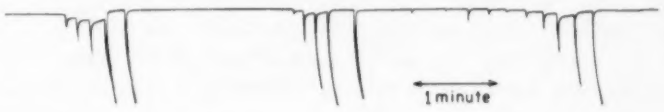

Fig. 26.—Dog 170-B: midpontine transection, followed by vagotomy and the appearance of apneustic breathing. Five milligrams of racemorphan abolished this pattern in favor of Biot's breathing, which persisted for 90 minutes, until a second dose of racemorphan reestablished nonperiodic breathing. This particular variation of periodic breathing shows a one-sided crescendo pattern, the first breaths being small, with a more or less progressive increase to a maximum. Inspiration down.

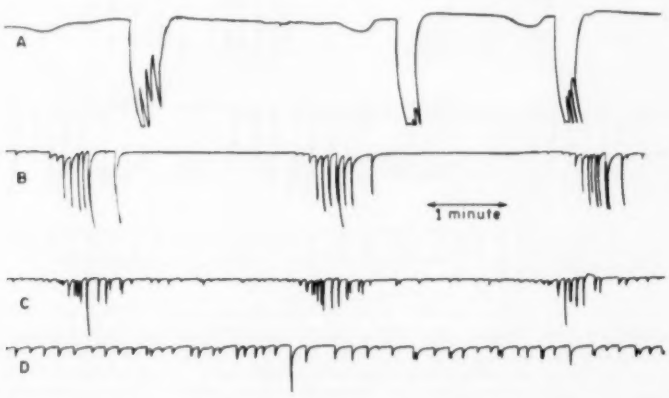

Fig. 27.—Dog 226-B: midpontine decerebration followed by vagotomy, producing typical apneustic breathing (*A*). Further transection of the brain stem converted the pattern to Biot's breathing. Five milligrams of racemorphan reduced the all-over amplitude and produced an element of waxing and waning having some resemblance to Cheyne-Stokes respiration (*B*). Later, small breaths appeared throughout the cycle (*C*). Nearly two hours later, the larger breaths, as well as the periodicity, had almost completely disappeared, and the usual ataxic medullary respiration remained. This pattern continued during the subsequent survival period of 3 hours and 25 minutes.

B the same periodicity is preserved after the apneustic component has been abolished by a further transection just below the pons. A minor degree of incrementation is seen at the onset of these breath groups. Five milligrams of racemorphan reduced the all-over amplitude of the grouped breaths without changing the periodicity; small breaths appeared throughout the whole of the previous phases, and obvious waxing and waning of the grouped breaths developed (*C*). This pattern is clearly more closely related to Cheyne-Stokes respiration than to Biot's breathing, but its

kinship to Biot's breathing is undeniable, as is its relationship to the apneustic breathing from which they both were derived.

The medullary type of breathing seen in Figure 28*A* is obviously not without some imperfect periodicity in amplitude, but a definite periodicity emerges in *B*, after an apneic dose of 10 mg. of racemorphan given in *A*. A second dose in *B* produced an unmistakable crescendo-diminuendo pattern in *C*, which was retained in *D* after a third dose of racemorphan abolished the apneic intervals themselves.

In the experiment recorded in Figure 29 no drugs were given, but Biot's breathing developed after a transection within the trapezoid bodies, which spontaneously passed through an evolution similar to that in Figures 27 and 28 during the ensuing 70 seconds, as seen in *A* to *D*. As the amplitude of the grouped respirations diminished, the previously completely apneic intervals were filled more and more with small breaths, and waxing and waning became increasingly marked. Later, the periodicity gradually faded away in the ataxic breathing of medullary respiration.

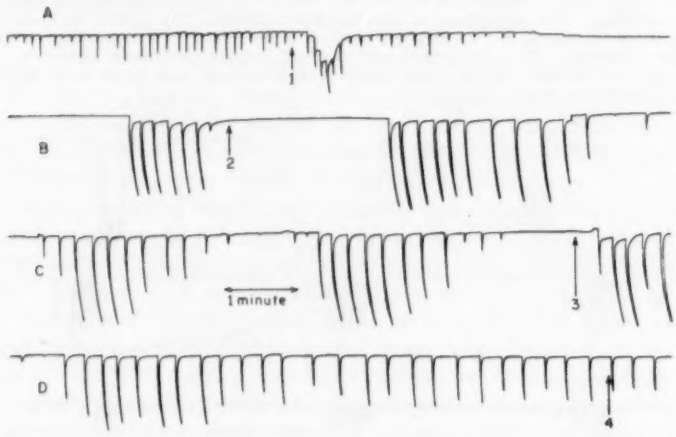

Fig. 28.—Dog 157-B: This animal had a classic midcollicular decerebration, but from the pattern of breathing that developed it is apparent that there had been some brain stem damage, accounting for the ataxic, medullary type of breathing seen in *A*. Appropriately for a medullary animal, 10 mg. of racemorphan (Arrow *1*) produced a short period of apnea, followed by Biot's breathing (*B*). In *B* (Arrow *2*) a further dose of 10 mg. of racemorphan altered the pattern to the clear-cut crescendo-diminuendo pattern seen in *C*. A third similar dose at Arrow *3*, in *C*, abolished the periods of apnea, although the phasic changes in amplitude persisted, as seen in *D*. A final dose terminated the experiment by apnea (Arrow *4*).

These experiments provide a clue to the relationship between Biot's and Cheyne-Stokes breathing, for in all of them there has been an element of suppression of the basic periodicity, which was not as sharply expressed as in Biot's breathing and which later faded away into medullary breathing. Apparently, then, the strongly expressed Biot's breathing is followed by an equally strong period of apnea, which may partly be an indication of central inhibition, refractoriness, or subnormality engendered by the discharge itself. As the central processes giving rise to the breathing phase diminish, the reciprocal inhibition of breathing during the subsequent phase is equally diminished, and the apneic interval becomes one of depression, and not suppression, of breathing. The appearance of nonperiodic ataxic medullary breath-

ing as the final stage is consistent with the analysis of Cheyne-Stokes breathing as a stage of slighter accentuation of the fundamental periodicity, transitional from Biot's breathing to the physiologically simplest pattern of nonperiodic, medullary breathing.

This assessment of Cheyne-Stokes breathing as a member of a family of periodic variations in breathing resulting from some form of "functional decerebration" differentially inactivating a hierarchy of suppressor circuits within the reticulum of the brain stem, releasing a basic rhythm intrinsic to the reticular facilitatory system, and finding expression in spheres of regulation other than the purely respiratory, provides for the first time a unified concept of the whole syndrome of Cheyne-Stokes breathing.

It was perhaps Traube [24] who first emphasized that in reality Cheyne-Stokes respiration is a part of a syndrome, and not an isolated sign restricted to the respiratory system, pointing out the frequent association of the respiratory phenomenon

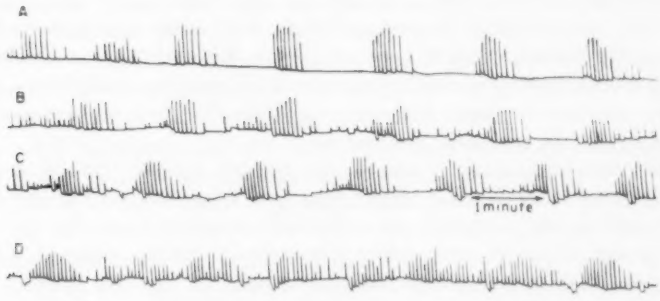

Fig. 29.—Dog 300-B: midcollicular decerebration, followed immediately by transection just below the trapezoid bodies. A period of apnea of 30 minutes ensued, with ventilation by reflex respiration. As breathing began, it assumed the character of Biot's breathing, except that, as seen in *A*, there is already a suggestion of waxing and waning in amplitude, and within the next 10 minutes this became more pronounced and highly suggestive of Cheyne-Stokes respiration. Vagotomy 20 minutes later (*B*) did not alter the pattern, which after 30 minutes began to lose its cyclic character, though it can still be recognized in *D*. The animal was killed by a 20 mg. intravenous dose of racemorphan 20 minutes after *D* was taken.

with changes in heart rate, blood pressure, pupillary diameter, somatic muscular tension, and consciousness. Lévy and Kæppelin,[25] reviewing these associated phenomena in 1898, classified them as (*a*) circulatory, (*b*) pupillary, (*c*) muscular, (*d*) reflex, and (*e*) mental symptoms. Among the circulatory phenomena were included changes in blood pressure, which was lower during apnea and higher during the breathing phase, and a variation in heart rate, with an interval of slowing just before the dyspneic stage. Although not all authors have since agreed on the exact linkage of the bradycardia to the respiratory phase of the cycle, its existence as a state of vagal hypertonia has been universally recognized, and many examples of extreme slowing and arrest of the heart beat, and various stages of A-V block have

been recognized. Less apparent signs of vasomotor disturbance have been noticed, e. g., pallor of the skin and of the mucous membranes at the end of the apneic interval, and depression of the fontanelles in infants.

During apnea the pupils may become contracted to pinpoints and insensitive to light, while with resumption of breathing they dilate and again react to light. There may occur conjugate deviation of the eyes, as well as nystagmus, during the apneic period. A variety of muscular signs have been recorded—conclusive movements localized in the face or arms, spasmodic contractions of the face, etc. There may be an increase in muscular tonus during the dyspneic phase, giving the appearance of rigidity during the phase of breathing and relaxation during apnea. Rarely, changes in sensation have been reported, with hyperesthesia during the period of respiration and anesthesia during apnea. Some authors have noted particularly an insensitivity to touch and pain during apnea. Tendon and patellar reflexes have been noted to disappear during apnea and to be exaggerated during the phase of respiration. During the apneic phase the patient may sleep or appear unconscious, while he will often awaken during the respiratory phase, become loquacious and even agitated, and have hallucinations and terrifying visions.

While there can be no doubt that the period of apnea imposes a chemical strain of considerable moment on all of these systems, which admittedly might produce a part of the total syndrome as observed in any single patient and almost certainly alters the total picture in its various details, it is equally true that the fundamental syndrome is not secondary to cyclic changes in oxygen supply and CO_2 elimination during the alternating periods of apnea and dyspnea, for artificial respiration with oxygen and other measures designed to minimize the effects of the respiratory deficit do not abolish the associated phenomena.

This fact Langendorff [26] emphasized as long ago as 1885, in describing the periodic behavior of the asphyxiated frog. Just before the phase of breathing began, the animal, which throughout the period of apnea had lain as though dead, began to show signs of motor unrest, which increased as breathing began. The frog righted itself, hopped about, and changed its posture until, as breathing stopped, it again fell motionless and failed to right itself if turned upside down. Arrest of motion came abruptly with the end of breathing, and in whatever position the animal found itself at the instant, this arrest being strongly suggestive of the Cheyne-Stokes syndrome in man, in which a patient is often unable to complete what was begun just as breathing stopped. Slowing of the heart occurred as in humans, with the period of maximum vagal activity just before the first breath was taken. The lymph heart participated in this inhibition, stopping simultaneously just before the period of movement began and starting again after movements and respirations had ceased.

The most significant part of these experiments, apart from the obvious clarity with which the clinical syndrome was reproduced, is that the conditions of the experiment were such that the possibility of fluctuating changes in the various systems resulting from the periodic breathing itself was largely eliminated, as, for instance, by ligature of the truncus arteriosus. Much earlier, Traube remarked that artificial respiration did not prevent the convulsions or other signs of somatic motor unrest that signal the end of apnea and usher in a new cycle of respiration. In most of the experiments reported here artificial respiration was also maintained, and while it understandably contributed to survivals, it did not alter the fundamental pattern of the syndrome (Traube [27]).

Such procedures, of course, not only would prevent any secondary changes resulting from the respiratory periodicity from affecting other centers in the brain but would effectively break up any reciprocal relations between the respiratory center and extrarespiratory systems, which have so often been invoked to explain the respiratory periodicity itself. Langendorff concluded, therefore, that "the various components of an attack are to be attributed to the coordinated results of periodic outbursts of stimulation within the gray matter of the brain and spinal cord."

Only within the last few of the 67 years that have intervened since Langendorff wrote this has the "gray matter" of the brain stem and cord been adequately appreciated as a fundamental integrative apparatus of the central nervous system, antedating the more precise system of ascending and descending tracts and clear-cut nuclear masses and providing the wide-flung and long-range support and background in which the functions of the other systems are embedded and out of which they develop.

While the subdivision of this reticular system subserving respiration is the only portion retaining obvious motor expression in the primate—and this greater degree of persistence of function is undoubtedly the reason the respiratory manifestations of Cheyne-Stokes breathing may be the only component of the syndrome seen in many patients—it is recognized that the activity of segmental reflex mechanisms and their receptivity to the descending impulses from the cortex are constantly adjusted by the impulses which filter downward from more rostral portions of the reticular system in medulla and brain stem. In this adjustment both inhibitory, or suppressor, and excitatory, or facilitatory, influences are recognizable, poorly differentiated anatomically in the spinal cord, but, from recent work, assignable to at least semi-specialized areas of the reticulum of the brain stem.

It is now firmly established that this system participates with equal importance in regulation within the spheres of respiration and autonomic control, providing indeed a mechanism by which these systems are inescapably linked and inevitably caused to operate as a whole in bodily activities. Much has been made of the concept that "the cortex thinks in terms of motion, not muscles." It is even more accurate to say that the brain "thinks" in terms of functions, for indeed motion is never a solitary expression, but is invariably bound up with a variety of activities in respiratory and autonomic spheres appropriate to it. Much has also been made of the principle of "irradiation" of reflexes. This it may be in the myopic view of a "simple" reflex, isolated anatomically or philosophically, but viewed from the standpoint of the whole organism "irradiation" is an expression of the impossibility of isolation within the central nervous system and of the refusal of the brain to deal with somatic, respiratory, and autonomic functions as completely separate systems. Undoubtedly, the reticular gray matter forms the anatomical substratum of "irradiation" and the most primitive means of patterning behavior. Willis,[28] thinking in terms of the "sympathy between parts," an idea which has bound up in it much of this same philosophy, wrote as follows (and his concept would be equally applicable today in discussing the direct and the diffuse portions of the central nervous system):

> But in the meantime, although there be singular passages, or channels of the animal Spirits of most Nerves, distinct among themselves; yet some do variously communicate with others through the branches and shoots sent on either side; which indeed ought to be so made, that when many Nerves together are required to some motion of a Muscle equally, all these, by reason of the commerce mutually had between themselves, might conspire in the same action; hence, in some motions of the members, as in the striking of a Harp or Lute and other complicated action,

many Muscles cooperate with admirable celerity; so that, although many be employed at once, they perform their task severally without confusion. Besides, there is need for the Nerves to communicate mutually among themselves, because of the Sympathetical motions of the members and of some of the parts, for neither for any other cause is the Nerve of the Diaphragm inserted into the brachial branches, or those belonging to the Arms, than that the exercise of living Creatures, especially in running or flying, might be proportionate to the tenour of Respiration. Hence it also proceeds, that in any passion, the Praecordia being bound up or dilated, the countenance and aspect of the face, yea and the gestures of the hands and members are pathetically figured. We have proposed sufficient Instances of this sort in our particular History of the Nerves, so that we need not here add anything more.

It is now recognized that this system of diffuse projections does not alone infiltrate the lower levels of the brain stem and spinal cord, where it serves as a common denominator of reflex activity, but that in an equally valid sense it permeates the higher reaches of the central nervous system, integrating cortex and thalamus, regulating the influence of the directly projecting systems, and thereby, in a very important manner, influencing sensation, awareness, the states of sleep and wakefulness, and consciousness and unconsciousness. If a fundamental fluctuation is envisaged within this system, normally held in check or, more correctly, counterbalanced by the suppressor mechanism, and released by differential inactivation of this system, it is understandable that during the "positive" phase there will occur respiratory activity and even hyperactivity, somatic unrest and vocalization, and autonomic changes, as evidences of the "descending" influence of this system, and hypersensitivity, hallucinations, and other sensory manifestations, along with restoration of consciousness, as manifestations of the upward projection of the same basic periodic changes. During the negative phase there would understandably be sleep or dulling of consciousness coincident with apnea, inhibition of somatic movements, and reversal of autonomic balance.

On this basis two of the outstanding characteristics of Cheyne-Stokes and related periodicities are understandable; i. e., the effect on periodicity of sleep and its potentiation or precipitation by narcotics, especially morphine. A normal function of the cortex is to activate the suppressor system; subcortical centers in the thalamus and hypothalamus contribute also. When the function on these regions ceases or diminishes, as occurs permanently in decerebration and reversibly in sleep and narcosis, the afferent input into the suppressor system is reduced and periodicity in breathing develops. Thus, in persons on the verge of Cheyne-Stokes breathing elimination of cortical suppression will precipitate the syndrome. It is known, of course, that morphine has a preponderant action on the multiple internuncial relay system of which the reticular system is constituted, and in the animal experiments reported here its very striking release of periodic mechanisms in the brain stem was its most characteristic property.

Equally understandable from this point of view is the observation that while sleep and narcotics may precipitate Cheyne-Stokes breathing, they may both cause it to disappear when they are deeper. If it is understood that periodicity is fundamentally superimposed upon nonperiodic medullary breathing and develops from an imbalance in the facilitation and suppression that regulate the medullary output, it follows that further diminution in higher control, either by deeper sleep or more profound narcosis, will depress the facilitatory system also and will restore balance at the simpler level of integration within the medulla, and periodic breathing will disappear.

The experiments reported, pointing as clearly as they do to an intrinsic rhythm generated within the brain stem reticulum and "released" through disequilibrium in a hierarchy of regulatory mechanisms within that system, leave little grounds, and no great need, for the multitude of hypotheses that have invoked some kind of reciprocal interaction between the respiratory system and systems external to it as the cause of the periodicity itself. It need not be denied that the changes in oxygen and carbon dioxide content of the blood and, secondarily, in blood pressure and cerebral blood flow will alter the form of the periodicity. They might conceivably reinforce it, although in the experiments reported here further anoxia usually abolished periodicity and reestablished regular breathing, but it seems unlikely that they participate in the genesis of the syndrome, in the postulated sense of a poorly damped servo mechanism.

VI. SUMMARY AND CONCLUSIONS

Periodicity in breathing is a reflection of an intrinsic slow rhythm of the brain stem normally expressed in deep, all-or-nothing, or gasping breathing.

When the respiratory system is at its lowest functional level of integration, i. e., without any higher-level regulation, breathing is nonperiodic. This is because the fundamental, primitive substratum of breathing is nonperiodic.

When the respiratory system is fully integrated, with all levels of supramedullary regulation in operation, from the upper reaches of the medulla to the cortex, breathing is also nonperiodic. This is because with full integration the slow rhythm is suppressed, through balancing of a hierarchy of suppressor and facilitatory systems.

At all levels in between, integration is incomplete, and the intrinsic slow rhythm is more facilitated than suppressed and finds expression in periodic breathing of one kind or another.

Depending on the degree to which suppressor and facilitatory systems are inactivated, a family of respiratory periodicities is created, including Biot's breathing, Cheyne-Stokes respiration, apneustic breathing, and decerebrate breathing.

Such differentiated inactivation with formation of periodic breathing may be produced by anatomical transection, by drugs of central action, by anoxia, by changes in circulation, and by a variety of other physiological and pathological circumstances, including sleep and psychological states.

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SPINAL CORD COMPRESSION STUDIES

IV. Outlook with Complete Paralysis in Man

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IT IS DESIRABLE, of course, to be able to predict the probable outcome of an illness with and without treatment. The physician can then evaluate therapy and inform the patient or his family and friends of the outlook.

Up to the present time, however, in cases of complete paralysis due to a spinal injury or a neoplasm it has been possible to make only a grave and uncertain prognosis. Generalizations on prognosis in such cases have been made, but they all share the weakness of not being accompanied by the evidence on which they were based. They, therefore, lack the precision necessary for them to be especially helpful clinically.

REVIEW OF LITERATURE

A. Spinal Cord Injuries.—In referring to traumatic lesions of the spinal cord, Alcock [13] cited Riddoch as saying, for example, that "immediately following the injury there may be absolute loss of function in the cord below the site of the injury. Later the clinical picture of anatomical transection may emerge or recovery may begin and continue up to a point at which the paralysis remains stationary and limited to certain limbs (L'hermitte)." This statement and the following one by Mixter [8] do not enable us to foretell when recovery may be expected:

> The prognosis of fractures of the cervical spine varies with the extent of the cord damage. With cord transection or softening there is no hope of return of function. . . . If the cord is not permanently injured recovery may take place.

Mixter noted that in general the prognosis was less grave in dorsal spine injuries and that "there is always some return of function" in lumbar spine injuries.

McAlpine [7] observed that "the longer the stage of spinal shock lasts the more likely is the cord to be completely severed. . . . In general, it may be stated that if the patient is going to regain useful power in the paralyzed limb and control over the bladder, he will do so within a month of the injury."

Grant [4] reported futile operations in 15 cases of cervical injuries with complete paralysis. The one patient who recovered was not operated upon.

Elsberg [1] cited a series of 314 cases of spinal cord injuries collected by Frazier. While no "recovery" occurred in any of the 93 patients with "complete transverse

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lesions," 18 are said to have "improved." Eighteen of 88 patients with "partial lesions" showed "recovery," and 46 were "improved." This report, again, is interesting but undocumented.

B. Spinal Cord Neoplasms.—The statements on recovery from complete paralysis caused by spinal cord tumors are also for the most part very general and lack both precision and documentation. Elsberg [2] wrote:

> Symptoms are relieved, the bedridden patient walks again, and the paralyzed and helpless resumes, in many cases, his former life of activity. . . . With severe symptoms and a history extending over a period exceeding 3 years, even with complete removal of tumor the chances of complete recovery are relatively slight, and even marked amelioration of symptoms does not occur very frequently. But even with a much longer history, if the severe symptoms are of brief duration, the results are frequently excellent.

To Elsberg the important factor in recovery after removal of spinal cord tumors was "not the duration of the disease from the first symptoms but the duration of the paralysis."

> A spastic paralysis of one or both limbs, even of many months' duration, can be completely recovered from in a few weeks or months. If the spastic paralysis has lasted more than two years, however, complete recovery is very rare and considerable spasticity is apt to remain. . . . One must, therefore, judge more from the physical signs and their duration than from the gross appearance of the cord at the level of spinal compression. . . . The duration of time that will elapse before marked improvement or complete recovery will occur varies in different patients. Often the improvement begins within a few hours of the operation and progresses rapidly. . . . In other patients the begining of improvement is delayed for weeks, and perhaps months. In one of my cases improvement began only after several years. When improvement had once begun, the progress continued steadily.

Grant [5] analyzed 108 cases of tumors, in 44 of which complete cures followed the tumor removal. He writes:

> It seems evident, therefore, that a case with spinal cord tumor who has been paralyzed for two months has better than an even chance for recovery, if the tumor can be removed without further damage to the cord.

C. Necessity for Operation.—Because of the gravity of the prognosis in cases of spinal cord or cauda equina compression by bone, muscle, tumor, or foreign body, knowing the best time to operate in such cases, or whether to operate at all, is of the greatest importance. Yet both questions are still controversial.

Some neurosurgeons believe that laminectomy is contraindicated in cases of fracture dislocation of the spine. Removing the vertebral spines and laminae and separating muscles and ligaments, they say, increase the instability of the vertebral column and the risk of additional trauma to the spinal cord.

Among those who favor decompressive laminectomy in these cases is Haynes,[6] who has advocated operation and removal of direct pressure at once, or certainly within the first 48 hours. He notes, however, that Col. R. Glen Spurling, at the Walter Reed General Hospital, and other qualified men at other centers were operating upon the unfortunates at a later date. "The results," Haynes writes, "seemed encouraging to them."

While also recognizing that the spinal cord should be decompressed as soon as possible, Pool * believes that, if necessary, decompression may be postponed for

* References 11 and 12.

several days without jeopardizing the chances for subsequent postoperative improvement. He makes the qualification, however, that "when complete sensorimotor loss up to the level of a cord injury lasts for more than five days, recovery is not likely despite laminectomy. This is less true of cauda equina lesions."

Munro [9] states that "cervical laminectomies should not be performed for seven to twelve days after injury. Lumbar laminectomies may be done if necessary twenty-four or forty-eight hours after injury depending on the patient's general condition." The basis for these recommendations is not given.

The question of the advisability of operation and the proper time for it, if it is advisable, also arises in cases of spinal cord edema and paralysis resulting from trauma. It is clinically impossible in such cases to tell whether the spinal cord has been severed or whether compression edema has only temporarily interrupted cord function. Treatment must be based on the assumption that these patients may recover.

Compression and edema are sometimes accompanied by hemorrhage and contusion of the spinal cord. In such cases irreversible neural damage may result partly from the trauma at the moment of impact and partly from mechanical deformation and the subsequent edema and its accompaniments. If the latter changes persist beyond a certain critical period, they may lead to irreversible destruction of neural elements. If it were somehow possible to relieve the compression and edema, the pathologic trend might be reversed and some recovery made.

PURPOSE OF INVESTIGATION

Material and Methods.—In the hope of supplying the precision necessary to validate generalizations on prognosis in cases of spinal cord or cauda equina compression and of providing the evidence necessary to determine whether or not to operate, and if so when, we present here a summary analysis of (*a*) 35 cases of complete spinal paralysis of traumatic origin, including 9 control cases in which operation was not done, (*b*) 27 cases of complete paralysis due to extradural spinal tumors, of which 6 surgically unexplored cases served as controls, and (*c*) 10 cases of complete paralysis due to intradural, benign encapsulated tumors. This series of 37 cases of complete paralysis and loss of sensation caused by spinal cord tumors was obtained from a series of approximately 1,500 cases of spinal cord tumors reviewed. We utilized only those cases in which repeated reliable examinations confirmed the presence of complete loss of motor power and sensation. A large number of cases were eliminated in which, in spite of the assurance of the patient to the contrary, some function, however slight, was reported in the affected parts by the examiner. The following factors were considered important in evaluating recovery after operation in our cases: (1) period of evolution of symptoms; (2) duration of complete paralysis; (3) onset of complete paralysis, whether sudden or gradual; (4) type of removal of neoplasm, whether complete or not, and (5) condition of spinal cord if visualized at operation. In discussing each group of cases we bring to bear the comparative evidence of our animal experiments, presented in Parts II [15] and III [16] of this series of investigations. In each discussion the pertinent clinical results of other writers are weighed.

TABLE 1.—*Fracture Dislocations with Immediate Complete Loss of Motor Power and Sensation Below Level of Lesion*

Age of Patient	Level of Lesion	Type of Injury	Roentgenologic Abnormality	Manometric Block	Duration of Paralysis Before Operation	Operation: Dura Opened	Operation: Degree of Cord Damage	Result	Period of Postoperative Follow-Up
28	T8	Gunshot wound	Fracture of spine and lamina	Not tested	1 day	No	Uncertain; minimal pulsation	No recovery	7 mo.
21	T10-L1	Gunshot wound	Fracture dislocation	Not tested	8 days	No	Cord compressed by fractured vertebrae; bone fragments removed	No recovery	14 mo.
19	T3-T4	Gunshot wound	Fracture of lamina and articular facets	Absent	22 days	Yes; intact	Epidural fat contused; arachnoid thickened and milky; cord soft	No recovery	3 mo. 11 days
29	T5-T7	Gunshot wound	Compound comminuted depressed fracture of spines and laminae	Not tested	1 day	Yes; torn	Bone fragments in spinal cord, severely contused	No recovery	8 mo.
39	T5	Shrapnel wound	Fracture	Not tested	22 days	Yes	Arachnoid adhesions; cord appeared normal	No recovery	7 yr.
61	T12	Fall from ladder	Fracture	Not tested	"Few hours"	Yes	Cord not pulsatile	No recovery	4 mo.
26	T6	Gunshot wound	Bony fragments in spinal canal	Not tested	8 days	Yes	Some fragments of bone removed and others left in spinal cord	No recovery	2 yr. 11 mo.
31	T10	Gunshot wound	Not recorded	Not tested	1 day	No	Complete transection of spinal cord	No recovery	5 yr. 10 mo.
40	T7	Shrapnel wound	Bony fragments in spinal canal	Not tested	"Few hours"	No	Bone fragments removed from spinal canal	No recovery	7 yr. 10 mo.
24	C5-C6	Dive in shallow water	Fracture dislocation	Complete block	14 days	No	Compression of dural sac by bone; cord pulsatile	No recovery	4 yr. 5 mo.
20	C7	Automobile accident	Fracture	Block?	3 days	Yes	No pulsation of dural sac; spinal cord yellow and swollen	Movements of arms and fingers better than before operation; no recovery of lower limbs	1 yr.

33	C5-C6	Automobile accident	Dislocation	Partial block	1 yr.	Yes	Bluish discoloration of cord; no pulsation	No recovery	1 yr. 5 mo.
37	T12	Automobile accident	Compression	Not tested	1 day	No	Compression of spinal cord by torn ligamentum flavum	No recovery	8 yr.
31	T4	Gunshot wound	Not recorded	Complete block	2 wk.	?	?	No recovery	5½ yr.
27	T12	Gunshot wound	Foreign bodies in spinal canal	Not tested	"Same day" 18 days	Torn	Dura torn; pus present; bone fragments removed	No recovery	14 mo.
29	T6	Gunshot wound	Metallic fragments in spinal canal	Not tested	13 days	Torn	Spinal cord almost completely transected	No recovery	2 yr. 3 mo.
26	T10-T12	Shrapnel wound	Compressed fracture	Not tested	1 day	Yes	Complete transection of spinal cord	No recovery	6 yr. 2 mo.
35	C6-C7	"Penetrating wound"	Fracture of articular facets and laminae	Complete block	19 days	Yes	Complete transection of spinal cord	No recovery	1 yr. 1 mo.
18	T10	Shrapnel wound	Not recorded	Not tested	7 days	Not removed	Complete transection of spinal cord	No recovery	6 mo.
43	T10-L1	Crushing injury	Compound comminuted fracture dislocation	Not tested	2 days	Torn	Complete transection of spinal cord	No recovery	7 yr.
40	T10	Shrapnel fragment	Fracture of spine and lamina	Not tested	1 day	Torn	Dura torn; spinal cord partially transected	No recovery	7 yr.
27	T7-T8	Gunshot wound	Fracture of lamina	Not tested	18 days	Intact	Spinal cord not pulsatile	No recovery	5½ mo.
25	T10-T11	Shrapnel wound	Comminuted fracture of spine and lamina	Partial block	7 days	Yes	Contusion and hemorrhage of epidural fat; shrapnel in epidural space; spinal cord yellowish and contused	No recovery	14 mo.
23	C5	Dive in shallow water	Fracture dislocation	Not tested	3 hr. 13 mo.	Yes Yes	Spinal cord severely mashed Spinal cord soft and cystic	No recovery	1 yr. 4 mo. after second operation
43	T12 L1-L2	Crushing wound	Comminuted fracture	Not tested	5½ mo.	Yes	Spinal cord shrunken; "total loss"	No recovery	2 wk. after operation; 6 mo. after injury
55	L1-L2, cauda	Airplane smash-up	Fracture of body and transverse process	Complete block	"Same day" 2½ yr. 4 yr.	....	Spinal fusion done Nerve roots freed from adhesions Anterolateral chordotomy for intractable pain	No recovery	4 yr.

RESULTS

A. Acute Traumatic Spinal Paralysis.—Table 1 shows our analysis of 26 cases of complete spinal paralysis of traumatic origin (fractures, dislocations, and bullet or shrapnel wounds). The location of the lesion varied from the fifth cervical to the second lumbar vertebra. The cervical, thoracic, and lumbar vertebrae were involved in 5, 18, and 3 cases, respectively. The paralysis was immediate in all cases. Complete spinal manometric blocks were recorded in four cases. Laminectomy was done on all patients, the post-traumatic intervals varying from three hours to one year.

The operative findings varied from compression of the spinal cord by fragments of bone to contusion and laceration and complete spinal cord transection. The operation was performed in 11 cases on the same day or the day following the accident, in 17 cases within the first 8 days, in 24 cases within the first 22 days, and only in 2 cases after 5½ months and 1 year. The dura was torn as the result of the injury in 5 cases, opened in 11 cases, and not opened in 5 cases. In five cases this information was lacking.

The postoperative follow-up periods varied from two weeks to seven years. Complete paralysis persisted in all patients, and recovery of functions was not observed except in two cases, in which some recovery of motor function occurred in muscles innervated by decompressed nerve roots just above the level of the cord injury. Also, in totally paralyzed and anesthetic limbs, paresthesias and phantom pain sometimes appeared, as recently described by Pollock and his associates.[10] We have reviewed a control series of nine surgically unexplored cases of spine injuries in which complete sensorimotor paralysis immediately followed the injury. The patients ranged in age from 20 to 60 years, the level of the vertebral injury varied from C4 to T12, and the follow-up periods were 1 day (two cases), 4½ months, 5 months (two cases), 18 months, 7 years (two cases), and 8 years. Except for slight improvement in sensation and somewhat better activity of muscles supplied by nerve roots at or close to the level of the injury, there was no significant recovery in any case.

Comment: The above experience would seem to support Grant's conviction "that no complete cord lesion should be operated upon regardless of whether a complete block can be shown by the Queckenstedt test. In these cases laminectomy is a waste of time and causes the patient suffering from a useless operation. Laminectomy is indicated only when the neurological signs are progressive, block or no block, and whether or not there is roentgenologic evidence of bone pressure." Yet Grant implies "that very early operation in acute traumatic paralysis may be helpful." (He apparently refers to lesions incomplete at the time of the trauma.) "Unless the existing pressure on the cord is relieved within 18 hours," he writes, "the damage will be permanent."

One of us assisted at operation on two patients, upon whom laminectomies were done within Grant's time limit. When the dura was incised, the spinal cord oozed out of the dural opening. That recovery would have occurred in these patients if the dura had not been incised is uncertain.

No recovery followed laminectomy without dural incision in two of our patients (Cases 1 and 13), for example. These operations were done a day after injury. At operation both patients seemed likely to recover, because there was normal dural sac pulsation in one and compression of the dural sac by the torn ligamentum flavum in the other. Our animal experiments suggest that these operations might have been done too late. In Case 24, in which the first operation was done three hours after injury, the spinal cord was "severely mashed."

Elsberg [1] also points out:

> The outlook for a patient with a transverse or a marked lesion of the spinal cord due to trauma is always grave, although many individuals with partial lesions recover satisfactorily and others recover sufficiently to be able to resume their earning capacity. . . . The main amount of improvement after a spinal cord injury will occur within the first 6 months, and little functional improvement will occur after about one year has passed.

It is uncertain whether Elsberg's last statement refers to complete or partial spinal cord lesions. It is a fact of general experience that almost complete recovery can occur in patients markedly, but not entirely, paralyzed and anesthetic below the level of the injury. We have seen such recovery whether or not laminectomy was done. Certainly, recovery is not uncommon after incomplete spinal lesions.†

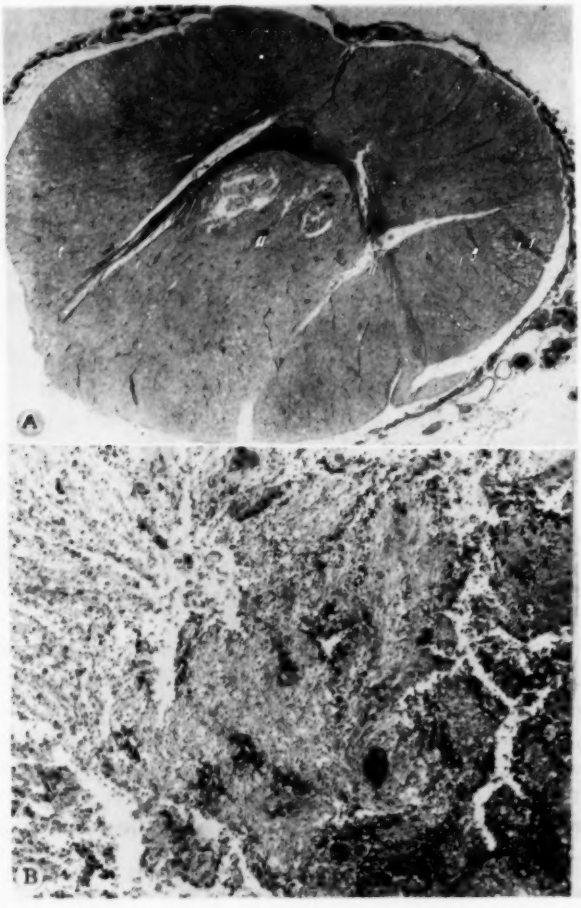
Elsberg correctly pointed out that extradural or intradural spinal hemorrhage rarely occurs without injury to the spinal cord. We should add that the spinal cord injury is usually the main cause of the patient's signs and symptoms. Our experience in animals and in man confirms Elsberg's statement that the chief types of spinal lesions that produce severe paralysis are hemorrhages into the spinal cord and destruction of cord tissue, at times complete pulpefaction.

Judged by such data as the foregoing, cases of complete paralysis following vertebral injuries seem to hold little hope. It was because of this bleak prognosis that we undertook our series of laboratory studies of spinal cord compression. We hoped that our findings might brighten the outlook.

Although the results of animal experiments cannot always be directly applied to man, they nevertheless form an important means of advancing our understanding and treatment of spinal cord injuries. Our researches on acute spinal cord compression in dogs show that recovery from complete loss of motor power and sensation may occur if the compression is removed early. Recovery depends, however, on the magnitude and duration of the compressive force. With great compressive forces, recovery of function occurs if the compression is released within five minutes.

† There are occasional reports of improvement after operations for complete paralysis due to spinal injuries. With the exception of two cases reported by Tinsley, these are not sufficiently documented with respect to the completeness of the paralysis, its exact time of onset, or the degree of improvement to permit accurate assessment. Tinsley's patients, aged 23 and 27 years, sustained injuries from high explosive shells, immediately after which there was evidence of complete transverse lesions at C7 and T11, respectively. Laminectomy was performed 22 hours and 27 hours, respectively, after injury. The dura had been lacerated, and foreign bodies were removed from the spinal canals. The first patient "was moving his toes and feet, position sense and touch was returning, there was a patchy return of sensation to pinprick." At the time of the last follow-up examination, 14 days after operation, the patient was "still on suprapubic drainage." The last follow-up report on the other patient was made 23 days after operation. Then "he was urinating spontaneously and moving his legs up to his knees. Sensation had returned to pinprick and touch, although it was patchy and incomplete."[17]

but not longer. With minimal spinal compressive forces, recovery occurs with periods of compression up to two hours. If pain sensation persists, however, complete loss of motor function may be followed by full recovery in dogs if the compressive force is released within three weeks, and probably even longer. The critical limits are longer in compression of the cauda equina in dogs. Great compressive



A, photomicrograph taken from a midthoracic segment of the spinal cord at the site of compression by a lymphosarcoma. Relatively little structural damage is present in spite of the complete lower limb paralysis.

B, photomicrograph taken from the cervical spinal cord underlying a fracture dislocation of C4 upon C5. Complete paralysis was present. Marked destruction of the spinal cord is seen.

Hematoxylin and eosin stains; *A*, × 9; *B*, × 43.

forces applied to the cauda equina for as long as five hours, and probably much longer, are compatible with full functional recovery after their release.

Disruption of the spinal cord and intramedullary hemorrhage result from the direct mechanical effect of the blow when great compressive forces are applied

to the spinal cord (Figure, *B*). The destruction of the spinal cord secondary to these rather immediate changes is accentuated by edema. Less compression produces less direct mechanical damage to the spinal cord, but the edema may contribute to the mechanical distortion or ischemia which accounts for the occasionally reversible effects on spinal cord function. The edema is marked within the first few days after compression. Doubtless the edema accentuates the effects of the compression in some cases and may constitute "the straw that breaks the camel's back." If compression is released before irreversible changes set in, function may be recovered.

On the basis of these laboratory researches, then, it seems reasonable to assume that after acute traumatic compression of the spinal cord in man spinal cord function can be recovered if the compressive lesion is removed before irreversible changes occur. If, moreover, the secondary edema could be prevented or its effect minimized by decompression, it is possible that, in some cases, complete destruction of the spinal cord could be averted and partial recovery of function secured. Whether the spinal cord changes leading to paralysis are irreversible cannot, of course, be determined by examination. For practical purposes it seems advisable to assume that the changes are reversible and to try as early as possible to remove a compressive lesion, such as a fragment of bone, a piece of cartilage, ligament, or muscle, a dislocated vertebra, or a foreign body.

In cases of spine injuries followed by immediate and complete loss of motor and sensory function, decompressive laminectomy should be promptly attempted if there is evidence of a spinal manometric block. Because simple reduction of the dislocation has not, in our experience, resulted in recovery from paralysis in any case, precious time should not be spent at such attempts.

In cases of total spinal paralysis where roentgenography reveals no abnormality of the spine, but where manometric examination shows complete spinal block, laminectomy should probably be done. When the dura is intact, it should not be opened because of the hazard of herniation of the softened spinal cord through the decompression. It appears wise, however, to split the outer layer of the dura to increase the efficacy of the decompression.

Probably few patients will come to the neurosurgeon within the critical time limit compatible with functional restoration, but those that do might well recover in competent hands. Confident prediction is, of course, impossible, but our experimental evidence indicates that these recommendations deserve a trial, especially since expectant treatment in cases of traumatic spinal lesions followed by immediate total sensory and motor loss offers no hope in our experience.‡

‡ In thinking back over our experience with traumatic spinal lesions, it seemed to us that we remembered patients who had recovered sensory and motor function that had been immediately and completely lost after spine injuries. Careful review of the hospital record, however, showed that in every one of these cases physiological spinal cord transection had been incomplete and that either slight motion or sensory perception had been present immediately after the injury. We know of no well-documented case in which the patient has recovered useful motor function, with or without operation, if there was immediate and complete loss of sensation and motion below the level of the spinal cord lesion. We have discussed this matter with several experienced neurosurgeons. On first thought they said that they had seen such cases. On further reflection, however, they admitted that some motion or sensation of the affected parts might have been present.

TABLE 2.—*Extradural Neoplasms (Thoracic) Causing Complete Paralysis of Sensory and Motor Function*

Histologic Diagnosis	Age, in Yr.	Duration of Motor Symptoms	Mode of Onset of Final Stage of Complete Paralysis	Duration of Complete Paralysis	Degree of Tumor Removal	Onset of Recovery	Result	Follow-Up Period
Lymphosarcoma 5 cases	44	5 mo.	1 day	2 mo.	Complete	1 day	Full recovery, 18 mo.	2 yr.
	37	12 days	Sudden (in 2 days)	10 days	Complete	9 days	Able to walk and control bowel and bladder function, 54 days	7 mo.
	65	4 mo.	2 wk.	5 wk.	Complete	11 days	Good foot dorsiflexion and thigh abduction, 22 days; no further follow-up	22 days
	24-46	4-13 days	Sudden (overnight)	2-12 days	Partial	.....	No recovery	9 days-1 mo.
Sarcomas 4 cases	16-61	1 wk.-2 mo.	Rapid advance of weakness leading to complete paralysis in 2 days; 1 wk.; 2 days; "sudden"	"Few days" to 2 wk.	Partial	.....	No recovery	19 days 7 mo.
Metastatic carcinoma 3 cases	44	5 wk.	Few days	4½ wk.	Partial	3 wk.	Able to walk and control bowel and bladder function, 3 mo.	3 mo.
	56	18 mo.	3 days	3 days	Partial	1 wk.	Able to move toes and ankles, 4 days	2 mo.
	51	11 days	Sudden (over night)	5 days	Partial	.....	No recovery	10 days-1 mo.
Myeloma 3 cases	54-63	2 wk.-1 yr.	"Sudden"; sudden (1 day); over night	1 day-3 wk.	Partial	.....	No recovery	10 days-1 mo.
Osteoid sarcoma	18	3 wk.	2 days	8 days	Complete	7 days	Walked without cane, 18 mo.; full recovery, 6½ yr.	7 yr.
Giant cell sarcoma	8	1 mo.	Sudden, after lumbar puncture	9 days	Complete	6 days	Full recovery, 1 yr.	4 yr.
Hypernephroma	17	11 days	Sudden (2 days)	8 days	Partial	.....	No recovery	3½ wk.
Chondroma	43	11 mo.	Uncertain	2 mo.	Partial	.....	No recovery	1 mo.
Ganglioneuroma	13	17 days	Rapid advance of weakness leading to complete paralysis in 2 days	12 days	Partial	.....	No recovery	2 mo.
"Neoplasm or tuberculoma"	25	2 wk.	Rapid advance of weakness leading to complete paralysis in 3 days	8 days	Partial	.....	No recovery	6 mo.

B. Progressive Complete Paralysis Due to Extradural Neoplasms.—Table 2 lists 21 cases of complete paralysis of the lower limbs alone or of both the lower and the upper limbs. In each case, the paralysis was of gradual onset and progressive course and was due to compression of the spinal cord by various tumors (Figure, *A*), chiefly malignant ones. Laminectomy was done in all cases. The third and fifth thoracic segments were each affected in nine cases; the sixth and ninth segments, in five. The other segments were affected from one to three times. The following types of neoplasm were encountered: lymphosarcoma (5 cases), myeloma (3 cases), metastatic carcinoma (3 cases), sarcoma (2 cases), and chondroma, ganglioneuroma, tuberculoma, liposarcoma, osteosarcoma, hypernephroma, giant cell sarcoma, and osteoid sarcoma, 1 case each.

The duration of symptoms leading to complete paralysis was calculated from the initial motor symptom referable to the tumor. Because the majority of these tumors were malignant and multiple pain was not considered a reliable criterion indicating the onset of symptoms referable to the spinal tumor, the paralysis might frequently have been due to damaged extraspinal rather than spinal structures. Although impaired motor power of the lower extremities was found to have existed for from 4 days to 18 months, in the majority of cases (14 out of 21) motor symptoms were noticed for less than 3 weeks. The onset of the final complete paralysis was usually described as sudden. Frequently it occurred overnight, once immediately after a spinal tap, after a day or two of rapid advance, and only once did it require as much as two weeks for the final stage of rapidly advancing complete paralysis. The interval between the appearance of complete paralysis and the operation varied from one day to two months. In the majority of cases, however, operation was performed during the first two weeks (16 out of 21, in 10 of which the interval fell within 10 days). The removal of the neoplasm was described by the surgeon as partial in 16 cases and complete in 5 cases.

The degree of recovery, if any, and its relation to the above-mentioned factors are of particular interest. There was some recovery of function in two cases (lymphosarcoma and metastatic carcinoma). If the follow-up period in these cases (22 days and 2 months, respectively) had been longer, more recovery might have occurred. There was good recovery in 5 patients and no recovery of function in 14. The likelihood of recovery, although not great in this series, seems to have been related to the completeness of the tumor removal. In 4 of the 5 patients in whom good recovery occurred, the tumor was completely removed, whereas in all of the 14 patients who failed to show any recovery the tumor was only partially removed. The tumor was a lymphosarcoma in two of the patients who showed good recovery, and in the other three the pathologic diagnoses were metastatic carcinoma, giant cell sarcoma, and osteoid sarcoma. The last two tumors were relatively benign, and the patients were alive when last seen, four and seven years after operation, respectively. Complete paralysis before operation in these patients lasted from eight days to two months. We surveyed a control series of six cases of metastatic carcinomas of the spine with surgical exploration in which complete paralysis occurred over intervals comparable to those listed in Table 2. The follow-up periods varied from six days to three months, during which intervals four patients died. No functional recovery occurred in any case.

C. Progressive Complete Paralysis Owing to Intradural Neoplasms.—Table 3 summarizes 10 cases of complete paralysis due to benign encapsulated tumors, all intradural (6 meningiomas and 4 perineurial fibroblastomas). The five patients with meningiomas that were completely removed have shown considerable recovery; three are able to walk without assistance, and two with assistance. The symptoms in these patients lasted from 13 months to 10 years. The mode of onset of the final stage of complete paralysis was gradual in all cases except one, in which the paralysis became complete after a spinal puncture. The patients were completely paralyzed for from five weeks to seven months before operation.

One patient with a meningioma did not recover. Two factors are pertinent to this case: Complete paralysis had existed for 12 months, and only two-thirds of the tumor had been removed.

The four patients with perineurial fibroblastomas have improved to the point where they are able to walk without assistance. Two of the patients have recovered

TABLE 3.—*Extradural Encapsulated Fibroblastic Tumors* (Cervicothoracic) Causing Complete Sensory and Motor Paralysis*

Age, in Yr.	Duration of Symptoms	Duration of Complete Paralysis	Degree of Tumor Removal	Onset of Recovery, in Days	Result	Follow-Up Period
48	2½ yr.	12 mo.	Two-thirds	..	No recovery	13 mo.
70	2 yr.	2-3 mo.	Complete	9	Walks with assistance, 3 mo.	3 mo.
45	16 mo.	5-6 wk.	Complete	3	Walks well, 6 mo.	6 mo.
65	13 mo.	6-7 mo.	Complete	6	Walks well, 5 mo.	5 mo.
65	18 mo.	4 mo.	Complete	1	Full recovery, 5 mo.	5 mo.
73	10 yr.	6 mo.	Complete	2	Walks with assistance, 4 mo.; steadily improving	4 mo.
29	7½ mo.	40 days	Complete	1	Walks well, 46 days; full recovery, 9 yr.	9 yr.
41	3 yr.	3 mo.	One-half	2	Walks well, 33 days	43 days
41	1½ yr.	3 mo.	Complete	1	Walks with assistance, 3 mo.	4 mo.
41	5 yr.; recurrence, 6 mo.	1 mo. 2-3 wk.	Partial Complete	4 1	Full recovery, 6 mo. Walks well, 2 mo.	6 mo. 2 mo.

* The tumor was a meningioma in the first six cases and a perineurial fibroblastoma in the last four cases.

completely. The symptoms leading to complete paralysis in these patients lasted from one month to five years. These patients were completely paralyzed for from one to three months. In two patients, the tumor was not completely removed. In one patient, the tumor recurred five years later and was then completely removed. Again, the patient recovered and was able to walk. All patients regained urinary and fecal control.

D. Recovery of Walking Ability After Tumor Removal.—Table 4 lists those totally paralyzed patients who became able to walk after their tumors, which had caused spinal cord compression, were removed. At operation the tumor removal was thought to be complete in all but one case (metastatic carcinoma). The 13 cases are arranged in the order of duration of symptoms. Recovery of function began 1 to 14 days after operation in these cases. Motor recovery was recorded first in seven cases, motor and pain sensation returned together in three cases, and pain recovery preceded motor recovery in three cases (one patient was operated upon twice and recovered excellently each time). The return of other forms of sensation

was slower.§ Urinary control began to return from one day to two months after operation. The patients were able to walk from 17 days to 5 months after operation.

The longest period of delay in walking was four and one-half months, in Case 1. It is of considerable interest that this patient showed the shortest duration of symptoms (three weeks). He continued to improve, however, for seven years after operation. At that time his walking ability and his general condition were described as "excellent."

The patient whose symptoms lasted a very long time (five years, Case 12) was able to walk in the shortest time after operation. He began walking in 17 days and reached "a normal state" in 6 months.

TABLE 4.—*Ambulatory Patients After Removal of Spinal Cord Tumors Causing Complete Paralysis (Listed in Order of Duration of Symptoms)*

Histologic Diagnosis	Age, in Yr.	Duration of Symptoms	Duration of Complete Paralysis	Onset of Recovery, in Days	Walking Time	Follow-Up Period
Osteoid sarcoma	18	3 wk.	8 days	7	With cane, 14 mo.; normally, 7 yr.	7 yr.
Giant cell sarcoma	8	1 mo.	9 days	6	Without assistance, 2½ mo.	4 yr.
Lymphosarcoma	37	2½ mo.	10 days	9	Without assistance, 54 days	7 mo.
Lymphosarcoma	44	7 mo.	2 mo.	1	Without assistance, 6½ mo.	2 yr.
Perineurial fibroblastoma	29	7½ mo.	40 days	1	Without assistance, 47 days	9-5/6 yr.
Metastatic carcinoma	44	1 yr.	4½ wk.	14	Without assistance, 35 days	3 mo.
Meningioma	65	13 mo.	6-7 mo.	6	With assistance, 38 days; without assistance, 5 mo.	5 mo.
Meningioma	45	16 mo.	5-6 wk.	5	Without assistance, 25 days	6 mo.
Perineurial fibroblastoma	41	1½ yr.	3 mo.	1	Without assistance, 4 mo.	4 mo.
Meningioma	65	18 mo.	4 mo.	1	Without assistance, 2 mo.	5 mo.
Meningioma	70	2 yr.	2-3 mo.	9	With assistance, 3 mo.	3 mo.
Perineurial fibroblastoma	41	5 yr.	1 mo.	4	With assistance, 17 days; normally, 6 mo.	6 mo.
		Recurrence 4½ yr. later				
	..	6 mo.	2-3 wk.	1	Without assistance, 52 days	3½ mo.
Meningioma	73	10 yr.	6 mo.	2	With cane, 3½ mo.	3½ mo.

COMMENT

It is difficult nowadays to obtain for case study patients who have been completely paralyzed by spinal cord tumors. Most of them prove to have rapidly growing malignant tumors. We have only eight cases in which benign encapsulated tumors of the spinal cord caused complete paralysis and were completely removed at operation. It is a tribute to physicians that the correct diagnosis in such cases is now made long before the stage of total paralysis. There are four additional cases of tumors that were not of the benign encapsulated type but were, nevertheless, thought to have been totally removed at operation. Our series of completely paralyzed patients in whom total tumor removal was possible is small, 12.

§ It is possible that a special interest in time of return of sensory, motor, and autonomic functions in these cases at the time of observation might have yielded more precise and reliable information about the sequence of their return.

The 1st and 12th cases in Table 4 show the shortest (8 days) and the second longest (5 years) duration of symptoms and, respectively, the longest (4½ months) and the shortest (17 days) delay in walking after tumor removal. This observation, although gleaned, to be sure, from a very small number of cases, gains significance in the light of our animal experiments, which likewise show that the shorter the period of time required to produce complete paralysis the more delay in, and the less likelihood of, recovery. Another factor in this evaluation, however, is the duration of the complete paralysis. Duration was longest (12 months) in Case 6 (Table 3), which showed no recovery whatever. Among the patients who did recover, duration of complete paralysis was longest (six or seven months) in Case 6 (Table 4). The patient was able to walk without assistance five months after operation.

The patient who became completely paralyzed over the longest period of time (10 years) now walks with a cane, three and a half months after operation; and she is still steadily improving. It is significant that she showed one of the longest periods of complete paralysis (six months) before operation.

The opposing interplay of these two factors, clearly demonstrated in the dog, is indicated in the two lymphosarcoma cases, both in the same age group, listed in Table 4. The second case showed a period of symptom evolution approximately three times as long as that of the first case. On this basis one would expect a shorter recovery time. However, the recovery time was over three times as long, probably because the duration of complete paralysis was six times as long as that in the first case.

A rather short duration of symptoms leading to complete paralysis occurred in the group of extradural malignant neoplasms, in which good recovery occurred in but 3 of the 19 cases.‖ In fact, the final stage of complete paralysis in these cases occurred within but a few hours or a few days. In none of the cases of immediate total paralysis following spinal trauma did any recovery occur. On the other hand, recovery occurred in all but one completely paralyzed patient, in whom there were benign encapsulated tumors, preceded by a more gradual onset and course of symptoms. There can be no doubt, then, that the manner of onset of symptoms leading to complete paralysis is an important factor in the outcome of the paralysis when the compressive lesion is removed.

What accounts for this striking difference in recovery in these two groups of cases? Our studies ¶ suggest that in acute compression of the spinal cord paralysis may result from disruption of nerve tissue directly or by hemorrhage, as well as by mechanical deformation of neural structures rather than by ischemia. The resulting edema, however, may further impede nerve conduction directly or through interfering with blood supply.

In suggesting a possible treatment to aid in restoring nerve function in such cases, it is obvious that the factor of direct disruption of nerve tissue is beyond our reach. It is possible, however, that surgical attempts to relieve the compression,

‖ These results should be emphasized in view of the widespread pessimism concerning the outlook for patients paralyzed by malignant neoplasms. In all probability other patients in this series would have benefited too if early radical spinal tumor removal could have been carried out.

¶ References 3, 15, and 16.

edema, and ischemia might prove fruitful if the resultant damage to the nerve tissue has not become irreversible. This condition one cannot know in advance. For practical reasons, it becomes imperative to advocate the removal of compressive spinal lesions as early as possible in the hope of restoring spinal cord function.

Our clinical evidence suggests in the main a direct and inverse relationship, respectively, between the duration of symptoms and of paralysis, on the one hand, and the recovery process, on the other. However, the role played by each of these two factors in recovery is difficult to assess accurately in our few patients because of the interrelationship of multiple factors. In addition to the duration of the patient's illness and the duration of the complete paralysis, one must consider the patient's general health,# the degree of tumor removal, possible trauma to the spinal cord at operation, the treatment given his paralyzed muscles, and his cooperativeness. In the absence of such controlled clinical studies, which would require a large number of cases, one must rely chiefly on the results of animal experimentation, where most of the factors that affect the functional results of spinal cord compression can be controlled. These studies show clearly that recovery after removal of the compressive lesion is better in cases where the duration of symptoms is longer and complete paralysis is shorter. Our clinical studies also seem to point in this direction.

The outlook is poor for recovery of function in man after the acute onset of complete sensorimotor loss due to a spinal cord lesion except for the rare cases of spinal cord concussion.[12] When there was any evidence of spinal cord conduction through the area of the lesion, however, either sensory or motor, considerable, or even complete, restoration of function was observed. This observation was made in two men whose lower limbs immediately became completely paralyzed after midline herniated intervertebral discs had been removed at the second and the seventh thoracic levels, respectively. The first patient, however, felt pinprick applied to certain parts of his buttocks and genitalia. There was no other sensation. The second patient lost all sensation except for appreciation of vibration at the left knee and right iliac crest. Motor recovery began, respectively, on the 14th and 20th postoperative days. Recovery continued, and the patients were able to walk with canes approximately a year after operation.

One of us (I. M. T.) has had many other experiences illustrating the same point, namely, that the presence of even a little sensory or motor function below a spinal lesion that produces an acute clinical onset favorably alters the prognosis.

One patient with complete motor paralysis of the lower limbs recovered almost full sensory and motor function 38 days after removal of a giant cell tumor arising from the sixth thoracic spinal level and compressing the spinal cord at this level. In spite of her complete motor paralysis before operation, she was able to recognize some vibratory, tactile, and pain stimuli over the lower limbs.

We have had repeated examples in our experimental studies of the importance of the animal's general health in the recovery process. Recently one of our dogs was subjected to three days of thoracic spinal compression leading to complete paralysis. Spinal compression was then maintained for an additional three days, then released. The animal gradually recovered and was able to walk two weeks later. He then began refusing food and lost weight steadily. During this period he became increasingly weak and finally, when he became emaciated, lost all hind-limb function.

We observed considerable, or even complete, recovery of function in cases of injury of the cervical and lumbar portions of the spine also, when the loss of function after the injury was almost but not quite complete.*

SUMMARY AND CONCLUSIONS

Significant recovery of function was not observed after the acute onset of complete sensory and motor paralysis of spinal cord function due to trauma.

When, however, the paralysis below the level of the lesion is incomplete immediately after the trauma, considerable or almost complete functional recovery may occur, no matter how slight the post-traumatic preservation of function is.

In spite of the uniformly dismal results thus far achieved in treating immediate complete paralysis from acute spinal cord injuries, the results of animal experimentation show that in some cases recovery can occur if the compressive force is removed within a few hours after the accident. This procedure is hedged in by such narrow restrictions of time that it may find a very limited field of usefulness. Nevertheless, it should be carried out in suitable cases in man.

The prognosis in cases of spinal cord tumors followed by gradually increasing and finally complete sensory and motor paralysis is very good if the tumor, though it may be malignant, can be completely removed without damaging the spinal cord.

Functional recovery began within 9 days after operation in 12 of our 13 cases in which recovery was good, and 14 days after the tumor removal in the last case.

The longer the interval over which the paralysis occurs and the shorter the duration of complete paralysis, the sooner does recovery occur after removal of the compressing mass.

The more acute the onset of paralysis in such cases, the more urgent is an immediate attempt to alleviate the condition of the compressed spinal cord.

* We are now studying the recovery of function in cases of incomplete transverse spinal cord lesions of traumatic or neoplastic origin.

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POLIOMYELITIS

XII. Clinical Evaluation of Hypothalamic Involvement

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IN BULBAR poliomyelitis the hypothalamus shows evidence of microscopic damage in 85% of the cases. Clinical evidence of severe hypothalamic involvement in this disease is manifested by diverse symptomatology, including aberrations in temperature regulation, water metabolism, carbohydrate metabolism, cardiovascular control, and gastrointestinal activity. Since a large number of patients with bulbar poliomyelitis do have definite damage to the hypothalamic nuclei, one would expect many of the recovered patients to show some clinical evidence of such involvement. Unfortunately, there has been no single test or combination of tests which would enable one to adequately evaluate the status of this area of the nervous system.

Adjustment to our constantly changing environment is effectively carried out by the hypothalamus under normal circumstances. Although invested with considerable reserve through its complicated connections, the hypothalamus when damaged is unable to control bodily responses adequately. Because of the importance of this regulatory center to the body economy and the high percentage of cases of poliomyelitis with damage to this area, clinical evaluation of this region seemed pertinent.

In previous publications * a test battery was devised in an attempt to evaluate the hypothalamus through clinical and laboratory means. It was pointed out that in view of the complexity of this region, its connections, and multiplicity of functions no single test would be indicative of hypothalamic involvement. It was felt, however, that the abnormal responses to several tests in a battery of 10 or more, individually related to but not specific for hypothalamic function, would at least suggest involvement of a central regulatory center. Immediate criticism can be leveled at such an assumption in poliomyelitis, wherein the involvement is considerably more protean and involves widespread cerebral and cord damage with implication of sympathetic and parasympathetic fibers. The hypothalamus, however, remains the coordinating center of this vast autonomic system and even if peripheral autonomic fibers are damaged, endocrine-hormonal equilibriums are maintained.

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* References 1 and 2.

The role of the hypothalamus to the concept of stress and adaptation has been emphasized in recent years. Since stress can be exerted in innumerable forms, the test battery described below introduced this element, and the resulting responses were evaluated and compared with the responses of a control group.

PRESENT INVESTIGATION

The purpose of this communication is to reevaluate the test battery as an index of hypothalamic involvement and to determine whether or not such a battery can have any prognostic significance. The test battery was given to 47 patients with poliomyelitis, of whom 31 had bulbar and 16 had spinal involvement. Included in this battery were tests for postural adaptation, sweating, water metabolism, carbo-

TABLE 1.—*Results of Hypothalamic Test Battery*

		TEST	postural adaptation	sweat response	glucose tolerance	hemoglobin	b m r	r i u	cholesterol	eosinophil response: adrenalin	eosinophil response: insulin	eosinophil response: a c t h	eosinophil response: s e d	mecholyl	total no. patients
POLIO GROUP	bulbar	number tests given	26	27	22	29	24	22	25	26	25	20	24	17	31
		number tests abnormal	5	3	13	2	5	1	0	10	14	5	4	4	
		% abnormal	19	11	50	5	20	45	0	38	56	25	16	23	
	spinal	number tests given	14	9	13	16	13	15	14	17	16	15	14	13	16
		number tests abnormal	3	1	4	0	0	0	0	6	7	0	3	6	
		% abnormal	21	11	30	0	0	0	0	35	43	0	21	46	
CONTROL GROUP	normal	number tests given	3	5	3	5	6	1	4	3	3	3	2	2	6
		number tests abnormal	1	0	0	0	0	0	0	0	1	0	0	0	
		% abnormal	33	0	0	0	0	0	0	0	33	0	0	0	
	other cns dis	number tests given	9	11	12	12	10	6	12	12	12	9	2	1	14
		number tests abnormal	2	3	4	0	3	0	1	4	6	4	1	0	
		% abnormal	22	27	33	0	30	0	8	33	50	44	50	0	

hydrate metabolism, and endocrinopathic evaluation of hypophyseal-adrenal-thyroid relations. The effect of methacholine (Mecholyl) was also studied in these cases. The results of the test are shown in Table 1 and in individual tests separately discussed below. Fourteen patients with varying neurological disturbances and six normal subjects were used as controls.

Postural Adaptation.—Certain adjustments in circulatory dynamics are carried out when the body passes from the recumbent to the upright position. The normal response to such a change consists of a drop in systolic blood pressure of from 5 to 10 mm. Hg, with a return to the previous level within one minute; a rise in diastolic pressure; decreased pulse pressure, and an increased pulse rate. Because of the coordination of sympathetic and parasympathetic responses in effecting this change, the hypothalamus was considered to play a role.

Observations were made in 40 patients and could not be measured in 7 patients. Twenty-six of the patients had bulbar symptoms, and 14 had spinal symptoms only.

The response was considered abnormal in five of the bulbar group and in three of the spinal group, the percentages of abnormality being 19 and 21, respectively. The results are tabulated in Table 2.

In the entire test group only eight responses were abnormal, with a greater percentage of abnormality in the spinal group than in the bulbar group. It is to be pointed out that although bulbar poliomyelitis was accompanied in all cases by spinal involvement, the reverse did not occur. This would tend to negate further the abnormal responses of the bulbar group, since those observations could be the result of spinal cord involvement alone. The higher percentage of abnormal values in the spinal group would tend to implicate the descending sympathetic and parasympathetic tracts and their spinal outflows.

In an evaluation of postural blood pressure changes, the venous return, muscle activity, and status of the cardiac muscle must be considered. Since the venous return is largely dependent upon muscular contraction and intrathoracic pressures, any atrophy and weakness of trunk and limb muscles will affect cardiac output and cause abnormal responses. Electrocardiographic observations were not made, and the extent of myocardial involvement is not known.

TABLE 2.—*Postural Adaptation Responses*

	Poliomyelitis Group		Control Group	
Test	Bulbar	Spinal	Other C.N.S. Diseases	Normal
Number of tests	26	14	9	3
Abnormal	5	3	2	1
Normal	21	11	7	2
% abnormal	19	21	22	33

The actual drop in blood pressure following the attainment of the upright position is due in part to pooling of blood in the extremities, which results in a reduced venous return and lowered cardiac output. A drop in pressure of 10 mm. Hg is sufficient to stimulate the carotid sinus reflex, with a resultant increase in blood pressure and acceleration of the cardiac rate.

The effect of prolonged bed rest on this response must be considered. Taylor, Henschel, Brozek, and Keys [3] have demonstrated that a considerable period of time elapses before the normal response is attained after a prolonged period of bedfastness. In older subjects and in sick persons the recovery period for this response is even more protracted. Bed rest alone will produce an increasing tachycardia of 0.5 beat per day.

It is evident that this test has little value as an indicator of hypothalamic activity. Adjustments in positional circulatory dynamics can readily be made at the peripheral level without hypothalamic influence. While the low percentage of abnormal responses attests to its inadequacy, the higher percentage of abnormal responses among the spinal group indicates the lack of specific hypothalamic influence.

Temperature Regulation.—The hypothalamus, by controlling the autonomic nervous system and influencing ductless glands and skeletal muscles, is the main center of heat regulation. Heat conservation and dissipation centers have been postulated within the hypothalamus, and lesions in this area are accompanied by alterations in body temperature control. In bulbar poliomyelitis a number of patients

have been observed to manifest severe hypothermia and hyperthermia, and it has been postulated that these disturbances probably were due to hypothalamic involvement. While the hypothalamus is the principal controlling center of body temperature, muscular activity, sweat glands, blood vessels, and the adrenothyroid influences cannot be minimized, since they are the effector agents of heat control.

In the performance of the sweating test, heat applied externally to the body is the element of stress, and its effect is determined by the amount of sweat secretion. Twenty-seven patients with bulbar poliomyelitis and nine with spinal poliomyelitis were subjected to the sweating test. Of the bulbar group, three patients, or 11%, had an abnormal response, and 24 were normal. Only one patient, or 11%, with spinal poliomyelitis showed an abnormal test pattern. The percentage of abnormal responses was about the same in the two groups. Of the 36 patients on whom the test was performed, only 4, or 11%, gave abnormal responses. The results are tabulated in Table 3.

This test is dependent upon the application of heat, and the response of the body is evidenced by sweat secretion. Intact sweat glands are necessary elements of this test, and, since the status of the sweat glands is not known in poliomyelitis, the test cannot be accepted without reservations. The sweat glands are supplied

TABLE 3.—*Temperature Responses*

	Poliomyelitis Group		Control Group	
Test	Bulbar	Spinal	Other C.N.S. Diseases	Normal
Number of cases	27	9	11	5
Abnormal	3	1	3	0
Normal	24	9	8	5
% abnormal	11	11	27	0

by cholinergic fibers present in the sympathetic nerves. Secretion is produced by direct or reflex stimulation of the centers of the spinal cord, medulla, hypothalamus, or cerebral cortex. If medullary, pontine, or spinal lesions exist, the body is severed from influence of heat-regulating centers and therefore follows passively the temperature of its surroundings. It is well known that cervical cord, pontine, and medullary injuries show aberrations in temperature control, and the presence of bulbar and spinal involvement in our cases negates this test as an adequate, or even suggestive, indicator of hypothalamic involvement. Perhaps a more refined test would give more definitive information, although such a test would always be of questionable value in the presence of spinal and/or bulbar lesions.

Glucose Metabolism.—The control of carbohydrate metabolism, while not fully understood, is under the influence of many organs, including the pancreas, liver, thyroid, pituitary, adrenals, kidneys, and brain. The glucose tolerance curve has been used as an index of that metabolism, but since it is subject to many variables, the interpretation of blood sugar curves should be cautious. Normal gastrointestinal tract, liver, pancreas, adrenal, and kidney function must be assumed before such a test can point to the influence of the brain. The influence of the latter is exerted through parasympathetic, sympathetic, and hormonal channels. Vagal stimulation causes hypoglycemia, while hypoxia, emotions, and pentylenetetrazol (Metrazol) therapy produce a hyperglycemic state comparable to that effected by stimulation

of the posterior hypothalamic nuclei mediated through the adrenosympathetic axis. The hypothalamus maintains this balance between the vagoinsulin and the sympathetic-adrenal system.

The glucose tolerance curve was used in an attempt to evaluate this cerebral influence. Six-hour oral glucose tolerance curves were obtained from 35 patients in this series. Of these, 22 had bulbar and 13 spinal involvement. Abnormal curves were found for approximately half the patients. Of those with abnormal values, 13 had bulbar poliomyelitis and 4 had spinal involvement only. The results are expressed in Table 4.

This test would appear to be one of the best indicators of hypothalamic dysfunction. However, despite the greater frequency of abnormal curves in the bulbar group, one should insert a word of caution regarding the use of the oral glucose tolerance curve as an index of hypothalamic function, particularly as an individual test. As in the case of cardiovascular control and temperature regulation, the presence of spinal cord and bulbar lesions with sympathetic-vagal involvement may exert an influence on carbohydrate metabolism without implication of higher hypothalamic centers. Moreover, most of our abnormal tolerance curves were flat.

TABLE 4.—*Carbohydrate Metabolism Responses*

	Poliomyelitis Group		Control Group	
Test	Bulbar	Spinal	Other C.N.S. Diseases	Normal
Number of cases	22	13	12	3
Abnormal	13	4	4	0
Normal	8	10	8	3
% abnormal	50	30	33	0

Such a curve might result from poor absorption from the gastrointestinal tract, and gastrointestinal defects are commoner in bulbar than in spinal poliomyelitis. In addition, the dietary intake of this group, because of bulbar involvement, is poor, so that a state of relative starvation exists. Since elevated blood sugar values are the chief stimulus to insulin secretion, the insulin response may be minimal where absorption of glucose from the intact gastrointestinal tract is slow. In order to eliminate the variables of absorption, the intravenous route would provide a better test.

Methacholine (Mecholyl).—Methacholine has recently been employed as a test of hypothalamic function, although the exact mechanism of action is obscure.† The response to methacholine is chiefly parasympathetic but involves also sympathetic responses. The reaction to 10.0 mg. of methacholine chloride consists of sweating, lacrimation, salivation, and a rapid fall in systolic blood pressure, all of which appear within 20 to 60 seconds after injection. The diffuseness of the autonomic response implicates the hypothalamus, although no nuclear masses within that general area are specifically implicated. Blood pressure recordings are taken every one-half minute as the chief index of the patient's response.

This test was applied to 30 patients, 17 of whom had bulbar poliomyelitis and 13 spinal involvement only. The percentage of abnormal responses in the spinal

† References 4, 5, and 6.

group was nearly twice that of the bulbar group. Testing done in the control groups was insufficient to have any statistical value. The results are tabulated in Table 5.

The response to methacholine indicates a diffuse autonomic reaction. It is not necessary to postulate the hypothalamus as the instigator of this response. The greater number of abnormal reactions in the spinal poliomyelitis group would support this contention. While it is true that patients with spinal involvement only may have subclinical damage to the hypothalamus, it is reasonable to expect patients with overt brain stem symptomatology to have more evidence of hypothalamic involvement. Since this did not occur, it can be inferred that the test is not specific for hypothalamic damage.

Electroencephalography.—Electroencephalographic evidence of diencephalic or hypothalamic disturbance has been shown to be characterized by 14- and 6-per-second positive spikes. Bilaterally synchronous slow waves in frontal and parietal areas, although not specific of hypothalamic origin, are considered to arise from deep-related sources.

Electroencephalographic studies were performed on 24 patients with bulbar poliomyelitis and on 14 patients with spinal involvement. The number of abnormal tracings was rather low in both groups. There was no consistent abnormal electro-

TABLE 5.—*Results of Methacholine Responses*

Test	Poliomyelitis Group		Control Group	
	Bulbar	Spinal	Other C.N.S. Diseases	Normal
Number of cases	17	13	1	2
Abnormal	4	6	0	0
Normal	13	7	1	2
% abnormal	23	46	0	0

encephalographic pattern, and in no instance were positive spikes observed. Electroencephalographic tracings done on the control groups were insufficient to be of any statistical significance. The normal electroencephalographic pattern is, however, well recognized.

While the 14- and 6-per-second positive spikes have been noted in connection with other hypothalamic disturbances, there is as yet no agreement that this area serves as the focal point of such activity. Until more definitive studies of hypothalamic electroencephalographic patterns have been done, the use of the electroencephalogram as an index of such involvement must remain in abeyance.

I. HYPOTHALAMIC-ENDOCRINE RELATIONSHIPS

The adjustment of the internal milieu of the body is mediated through neural and hormonal means integrated in the hypothalamus. The more rapid neural reactions concerned with blood pressure and temperature regulation have been noted.

The influence of the hypothalamus upon the endocrine systems has received little attention until the recent developments of corticotropin and cortisone. The hypothalamus exerts its influence upon the endocrine system chiefly through the pituitary gland, with which it is intimately connected both anatomically and hormonally. The pituitary gland, acting as the master effector organ, regulates glandular activity by elaborating corticotropin, the adrenocortical hormone; the

follicular-stimulating hormone (FSH); the thyroid-stimulating hormone (TSH), and gonadotropic hormones. There apparently is a balance of these hormonal relationships, for a disturbance in one system is followed by adjustments in another. Such an example is to be found in the antagonistic actions of the pituitary adrenocortical hormone, corticotropin, to the pancreaticothyroid hormones, since it has been demonstrated by Thorn [7] that prolonged corticotropin therapy results in hypothyroidism and diabetes.

Although the exact mechanism of hypothalamic control over pituitary function remains obscure, the action is rendered through neural and vascular channels. Stalk-transmitted hypothalamic-hypophyseal connections are well known. Not so well known, but of equal importance, is a well-defined hypophyseal stalk portal system of veins, which surrounds the stalk and conveys blood to and from the hypothalamus. Whether neural impulses activate the pituitary to secrete corticotropin or whether the hypothalamus itself secretes the hormone is not certain. Scharrer,[8] Ibáñez,[9] and Roussy and Mosinger [10] have described secretory activity in the cells of the supraoptic and paraventricular nuclei. In addition, these nuclear areas are surrounded by a rich vascular network, and the secretion of hormonal

TABLE 6.—*Thyroid Responses*

Test	Poliomyelitis Group				Control Group			
	Bulbar		Spinal		Other C.N.S. Diseases			
	No. of Tests	% Abnormal	No. of Tests	% Abnormal	No. of Tests	% Abnormal	No. of Tests	% Abnormal
B. M. R.	24	20	13	0	10	30	6	0
Cholesterol	25	0	14	0	12	8	4	0
Radioactive iodine	22	4	14	0	6	0	1	0

substances into the blood stream by hypothalamic nuclei is anatomically possible.

Attempts were made to evaluate the hypothalamic influence upon the endocrine glands through an analysis of thyroid and adrenal activity. Functional tests of these target organs are well known and readily performed but are subject to recent doubt as to their adequacy.

Hypothalamus-Thyroid Relationships.—Mention has been made of the fact that thyroid activity is influenced primarily by pituitary secretions and to a less degree by adrenocortical secretions. The hypothalamic influence upon thyroid function is then mediated through the pituitary gland. While no known test of this relationship exists, it was felt that a survey of thyroid function in hypothalamic-damaged patients might indicate a faulty relationship. The basal metabolic rate, serum cholesterol, and radioactive iodine uptake were used as indicators of thyroid function.

The results of this survey are tabulated in Table 6.

The basal metabolic rate was performed in 24 instances of bulbar poliomyelitis and considered abnormal in 4 cases, or 20%. All the patients with spinal involvement only exhibited normal tests, while 30% of a control group with other disorders of the central nervous system showed abnormal basal metabolic rates.

The serum cholesterol was normal in all instances of poliomyelitis, whereas the control group exhibited elevated values in 8%. Radioactive iodine uptake was low in 4% of the test group, and no abnormalities were found within the control group.

The above results indicate very few abnormal values in the tests used. This would indicate that the hypothalamic influence upon thyroid activity is minimal or that the tests are inadequate. The latter is probably correct, since the basal metabolic rate at best can be used only as a rough screening test and the degree of thyroid dysfunction cannot be accurately predicted by the amount of negativity or positivity. The test itself is subject to many variables and has been widely criticized as a diagnostic aid because (1) it is not a direct measure of energy consumption, and only indirectly is it an index of thyroid function; (2) it depends upon the cooperation of the patient; (3) the basal state which is requisite is very difficult to attain, and (4) many patients with hypothyroidism and hyperthyroidism have normal basal values and, conversely, many normal subjects have high or low basal metabolic rates. Furthermore, many of the poliomyelitis patients tested were bedfast and had widespread muscle wasting. It is unjust to compare such persons with a normal standard and to interpret the result as indicative of thyroid dysfunction.

The serum cholesterol is often elevated in hypofunctioning thyroid states. The latter, however, is not the sole regulator of serum cholesterol, and, indeed, athyreotic persons may have normal cholesterol values. The absence of abnormalities in the test groups indicates its relative inadequacy.

The uptake of radioactive iodine by the thyroid has been shown to be in good agreement with the state of thyroid function.[11] The test is subject to the same vagaries as the basal metabolism rate and will not supplant the latter but, rather, will supplement it. Recent studies of thyroid dysfunction by means of this test have shed more light on this gland, and the test should not be abandoned. The tendency is to regard the thyroid in relation to other endocrine glands, such as the pituitary, adrenals, and pancreas, and to consider its relationship to the hypothalamus.

A more informative evaluation of thyroid function is to be obtained by analysis of the protein-bound iodine. This test should be used to evaluate thyroid-hypothalamic relationships.

Hypothalamic-Adrenocortical Relationships.—Although not fully understood, the hypothalamic-adrenocortical relationship has been the subject of considerable recent investigation, and there is general agreement that the adrenal cortex is activated by corticotropin elaborated by the anterior pituitary gland and that the hypothalamus is the chief regulator of corticotropin.‡ Gonadotropic hormonal secretion and ovulation in the rabbit were observed following stimulation of the tuber cinereum.[15] In 1950 Colfer, deGroot, and Harris [16] observed that rabbits exposed to stress developed a lymphopenia similar to that observed under corticotropin, and that whereas hypophysectomy abolished this response, denervation of the adrenal gland did not, thus indicating the humoral nature of this relationship. It was further noted that hypothalamic lesions in the posterior tuberal region and mammillary bodies abolished this response, while supraoptic lesions exerted no effect. Stimulation of mammillary bodies and the tuber cinereum resulted in a lymphopenia.[15] As a result of this, it has been postulated that lesions in this area of the hypothalamus effect the transmission of appropriate impulses to the median eminence; from this point the pituitary is activated by hormonal substances passing in the well-defined hypophyseal stalk portal system, in which the direction of blood flow is from the

‡ References 7, 8, 12, 13, and 14.

median eminence to the anterior pituitary.§ This and further observations indicate that blood levels of epinephrine and adrenal corticoids do not stimulate corticotropin by direct action upon anterior pituitary cells. There is, then, general agreement from all available evidence that corticotropin secretion is regulated by the hypothalamus.‖ It is likely that the adrenocorticoids exert a "hormonal feed-back" to the hypothalamus.

While this relation represents the normal physiologic response, there is some disagreement as to what activates the hypothalamic areas under conditions of stress, since other factors are brought into play, including cerebral cortical influences. For the moment it is apparent that the "normal" and "stress" phenomena are different. As originally planned, "stress" was to be applied in an evaluation of hypothalamic-adrenocortical relations by means of epinephrine and insulin. In the light of recent research ¶ Thorn and others have discarded the use of epinephrine as a valid test of this relationship. Epinephrine in the doses given here has little or no effect upon adrenocortical function, although in large doses there is a considerable effect.

The test as applied here consisted of an evaluation of the change in circulating eosinophiles four hours after the intramuscular injection of 25 mg. of corticotropin

TABLE 7.—*Eosinophile Response to Corticotropin, Epinephrine, and Insulin*

Group	Abnormal Responses, % of		
	Corticotropin, 25 Mg.*	Epinephrine, 0.3 Cc.†	Insulin, 0.15 Unit per Kg.
Bulbar poliomyelitis	25	38	56
Spinal poliomyelitis	0	35	43
Normal control	0	0	33
Other central nervous system diseases	44	33	50

* By intramuscular injection.
† By subcutaneous injection.

or the subcutaneous injection of 0.3 cc. of epinephrine or 1.5 units of insulin per kilogram of body weight. The results of these tests are tabulated in Table 7.

Although the percentage of abnormal tests is relatively high, no interpretation is possible in view of recent criticisms leveled against the employment of the circulating eosinophiles as the sole index of adrenocortical activation. Best, Muehrcke, and Kark [24] have demonstrated the inaccuracy of individual eosinophile counts and have observed a 50% reduction in circulating eosinophiles in healthy persons. Daily variations in circulating eosinophiles have been demonstrated by Halberg and associates.[25] Since the test as conducted here consisted of one determination, it has no proved value. Furthermore, intramuscularly administered corticotropin is partly deactivated. Thorn [21] as recently demonstrated the superiority of continuous corticotropin infusion over an eight-hour period, and he further advocated serial studies over two to three days as the most reliable test employing the 17-hydroxycorticoids as the index of adrenal activation.

In man there is no evidence that epinephrine is capable of eliciting a measurable increase in either 17-hydroxycorticoid excretion or eosinophile responses.# Thorn

§ References 13, 17, 18, and 19.
‖ References 13 and 15.
¶ References 20 through 24.
# References 20 through 23.

believes epinephrine may have a direct effect without implication of the adrenal cortex, since changes in the percentage of circulating eosinophiles is found in adrenalectomized animals. Furthermore, Darrow and Gellhorn [26] have demonstrated that hypothalamic activity is depressed by epinephrine, rather than activated by it.

Hume and Wittenstein [27] used epinephrine, insulin, and trauma as stress agents and employed the circulating eosinophiles as the index of the stress. Insulin, intramuscularly administered in doses of 0.15 unit per kilogram of body weight, causes a response similar to that of corticotropin under normal circumstances. Anterior hypothalamic lesions and paraventricular lesions abolished the response to insulin. The same animals, however, responded normally to corticotropin. This response was considered as evidence of continued maintenance of corticotropin output by the anterior pituitary lobe, but the latter is incapable of an increased secretion in response to stress. Thus, an intact hypothalamus is necessary for the increased release of corticotropin from the pituitary following stress. Stalk-transected animals show eosinopenic response; so Hume believes that the portal system is not necessary and that the hypothalamus is capable of its own secretion.

It is apparent that, regardless of the indications for the test, the means of measuring the response is unreliable. The eosinophilic response cannot be used as an index of adrenocortical function. The determination of urinary 17-hydroxy-

TABLE 8.—*Average Number of Abnormal Tests*

	Poliomyelitis		Control	
Group	Bulbar	Spinal	Normal	Other C.N.S. Diseases
Average no. of abnormal tests.....	2.0	1.9	0.3	2.6

corticoid or 17-ketosteroid excretion is the most reliable index of adrenocortical function. In this test battery collections for 17-ketosteroid excretions were made, but the values were not available at this time.

Water Metabolism.—Despite microscopic damage to the paraventricular and supraoptic nuclei, diabetes insipidus was not found in this group of cases. This would support the work of Harris [28] and Fisher, Ingram, and Ranson,[29] who have demonstrated the necessity of bilateral supraoptic lesions for the production of diabetes insipidus. At the onset of this investigation the Robinson-Kepler-Power test was used in an attempt to evaluate water metabolism. This soon appeared inadequate and was discarded. The hypertonic saline test, as outlined by Carter and Robbins,[30] was inaugurated, but insufficient values preclude its inclusion in this study.

II. BATTERY ANALYSIS

In the previous section the individual tests have been discussed, including the indications, results, and adequacy of each. Although individually these tests do not accurately indicate hypothalamic damage, abnormalities in several tests can be taken as an indication of dysfunction to this region. It was because of the multiplicity of known hypothalamic functions and the intricacy of its connections that single tests were considered inadequate and that a group of tests was devised.

Although a study of Table 8 shows more abnormalities in the bulbar group than in the spinal group or normal control group, an analysis of the total number

of abnormal tests in the battery in each group indicates the inadequacy of this battery, since in the bulbar group the average was 2.0 tests, while in the spinal group the average was 1.9 tests. The average number of abnormal tests in the control group was 0.3 and 2.6, respectively. These data are summarized in Table 8. The second control group in part consisted of persons with known hypothalamic damage as evidenced by other criteria. This accounts for the greater number of abnormalities in this group.

COMMENT

Although the relatively small average number of abnormal tests in the bulbar group is disappointing in view of the high percentage of cases with hypothalamic damage, this finding is merely the reflection of both the inadequacy of the individual tests and the inability to correlate microscopic changes with the degree of cellular function or dysfunction. One can conclude only that such a battery in its present form has little value as an index of hypothalamic function in poliomyelitis.

On the other hand, a glance at Table 1 shows more abnormalities in all the groups than in the normal control group. This observation suggests that a battery has merit and that as a weapon of diagnostic and prognostic aid it should not be abandoned. There is general agreement that the hypothalamus can be injured experimentally and that certain endocrine and neural alterations occur as a result of that injury. There is also general agreement that this area is subject to infections and traumatic and neoplastic processes, with consequent symptomatology. We choose, however, to evaluate that symptomatology which is obvious and to neglect that which is not obvious and which we cannot evaluate clinically. Why not, then, a test battery to evaluate suspected involvement which is not clear-cut?

Consideration of the need for such a battery and of the results of this preliminary experiment dictates a revision of this test group to include more informative tests and improvements in the technical performance of the old ones. Such a revised test battery has been under way at this institution. It includes the following tests:

1. Water metabolism, to be evaluated by means of the hypertonic saline and nicotine tests.* (This will evaluate the supraoptic-hypophyseal system.)
2. Adrenocortical relationships, to be evaluated by means of 17-hydroxycorticoid urinary excretion
3. Continuation of the blood glucose metabolism, but with the use of intravenously administered dextrose
4. Atropine test,[32] outlined by Hoffer
5. Evaluation of emotional responses
6. Determinations of serum protein-bound iodine

SUMMARY

Little doubt exists that hypothalamic lesions alone are capable of producing endocrine and metabolic changes, but the presence of bulbar and spinal involvement in the same patient renders it impossible to implicate the hypothalamus alone as the responsible source of the observed changes.

A preliminary study is presented in which a battery of 12 tests were used in an attempt to indicate hypothalamic damage in poliomyelitis.

* References 30 and 31.

The battery in its present form has limited value as an indicator of hypothalamic damage in poliomyelitis.

The need for a method of clinically evaluating the hypothalamus exists, and the concept of a test battery remains the most applicable at present.

A revised battery is presented.

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CIRCULATORY CONDITIONS IN ELECTROSHOCK THERAPY WITH AND WITHOUT A MUSCLE RELAXANT

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STUDIES on the effects of electroshock therapy on the circulation were made in 1943 by Gordh and Silfverskiöld [1] and by Silfverskiöld and Åmark.[2] They showed that electroshock therapy produced a considerable rise in the arterial blood pressure and a marked Valsalva effect, with a resulting rise in the venous pressure. Silfverskiöld and Åmark noted a rise in the arterial pressure of 80 to 120 mm. Hg. The venous pressure sometimes rose as high as 100 mm. Hg, or higher.

Altschule and associates [3] recorded a mean rise in the venous pressure of 42 mm. Hg in connection with electroshock therapy. Brown and associates * made recordings in dogs, monkeys, and human subjects during electroshocks. They demonstrated an initial fall in the blood pressure and the heart rate; it was followed, after about one second, by a rise above the basic values. In human subjects the systolic pressure rose on an average from 159 to 244 mm. Hg, and the pulse rate increased from 105 to 166 beats per minute.

Several investigations have been made on the effect of curarization on the arterial blood pressure in electroshock therapy. Woolley [7] observed blood pressures as high as 180 to 290 mm. Hg, most frequently from 200 to 220 mm. Hg, despite the administration of curare. Hobson and Prescott [8] found only a very slight rise in blood pressure when curare and thiopental sodium were given prior to the electroshock. Massion-Verniory and associates,[9] Donovan,[10] and Igersheimer and Stevenson [11] reported, on the contrary, a marked rise in blood pressure, although curare had been given. No study seems to have been made of the extent to which curarization modifies the venous pressure in electroshock therapy.

Disturbances in the rhythm of the heart are common in association with electroshock therapy and have been described by Bellet and associates,[12] Altschule and associates,[13] Craddock and Gilbert,[14] and Linn and Ottenheimer.[15] A study of the electrocardiograms in patients given electroshocks under partial curarization was made by Hejtmancik and associates.[16] They found a high incidence of arrhythmias,

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* References 4, 5, and 6.

most frequently in the form of ectopic beats, but seldom of a severe nature. Bankhead and associates [17] observed both vagal effects and ectopic beats, even when curare was used routinely. They recommended atropine and oxygen for the prevention of disturbances in the heart rhythm. Brody [18] suggested the administration of curare and oxygen, which he had found decreased the incidence of cardiac arrhythmias.

Thus, many authors have expressed the view that curarization affords some protection against sudden rises in blood pressure and other circulatory disturbances. The administration of curare preparations has, however, implied a considerable risk because of a long duration of action and, in certain cases, the circulatory effect. Succinylcholine iodide, a muscle relaxant with a short-term action and no appreciable toxic effects (Thesleff [19]), is now available. Consequently, we considered it of value to test the effect of practically total muscular relaxation produced by succinylcholine on the circulatory conditions in electroshock therapy.

METHODS

The femoral artery was punctured in seven male patients, and the intra-arterial blood pressure was recorded, using a mechanoelectronic transducer manometer (designed by Clemedson and Pettersson [20]). Each patient was given one electroshock (using Cerletti and Bini's technique and fixation of the patient) with the injection intravenously, one to two minutes beforehand, of 0.35 to 0.85 gm. of thiopental sodium (Pentothal) and 100 mg. of succinylcholine iodide (Celocurin). On a second occasion only the aforementioned dose of the barbiturate was given. In three of the patients, a third treatment was preceded by the administration, in addition to that of thiopental, of 0.3 mg. of succinylcholine iodide per kilogram of body weight, this being the dose used routinely in electroshock therapy (Holmberg and Thesleff [21]).

The venous pressure was recorded in eight patients, four men and four women, by puncturing a vein in the forearm with a cannula connected to an aneroid manometer. The quantity of succinylcholine iodide administered was either a total dose of 50 to 100 mg. or a dose of 0.15 to 0.25 mg. per kilogram of body weight. The latter dose has been found to be that usually resulting in a reduction in the strength of the convulsions by 40 to 50% (Holmberg, Hård, and Ramqvist [22]).

The cardiac rhythm was observed concurrently with the arterial blood pressure, both on the tonogram from the femoral artery and on an electrocardiogram recorded with an electroencephalograph.

Oxygen was always given in conjunction with succinylcholine. A subcutaneous injection of methylscopolamine nitrate (Skopyl), an agent with an atropine-like effect, was given 45 minutes before each electroshock.

RESULTS

With total muscular relaxation produced by 100 mg. of succinylcholine iodide, the maximal rise in blood pressure was—in all but one case, in which the rise was of the same magnitude—less than when no muscle relaxant was given. Without succinylcholine, the mean rise in the systolic blood pressure was from 116.9 to 204.7 mm. Hg, i. e., a rise of 87.9 mm. Hg. When succinylcholine was given, the mean rise was from 115.7 to 180.1 mm. Hg, i. e., a rise of 64.4 mm. Hg. The rise in blood pressure was 23.4 $\pm$ 7.01 mm. less with the use of succinylcholine; the difference is thus almost significant ($t = 3.34$; $d.\ f. = 6$; $P < 0.05$).

A striking feature was that the variations in the pulse pressure, which were sometimes extremely marked in ordinary electroshock therapy, were relatively small when succinylcholine had been given (Fig. 1). Nor was the rise in blood pressure so abrupt, and the jerky variations were lacking. Even 0.3 mg. of succinyl-

choline iodide per kilogram of body weight was sufficient to produce a certain leveling effect.

In all eight cases in which the venous pressure was recorded, the rise was considerably less with the larger dose (50 to 100 mg.) of succinylcholine iodide than without the administration of a muscle relaxant. In most of the cases (six out of eight) even the smaller dose was associated with a definitely smaller rise in the venous pressure (Fig. 2). In every case the rise in venous pressure was even and slow when succinylcholine had been given, whereas it could otherwise be extremely abrupt. Without succinylcholine, the mean rise in the venous pressure was from 17.5 to 52.0 mm. Hg in men and from 17.3 to 45.5 mm. Hg in women. When 50 to 100 mg. of succinylcholine iodide was given, the corresponding figures were from 14.8 to 19.0 mm. Hg in men and from 10.5 to 20.3 mm. Hg in women.

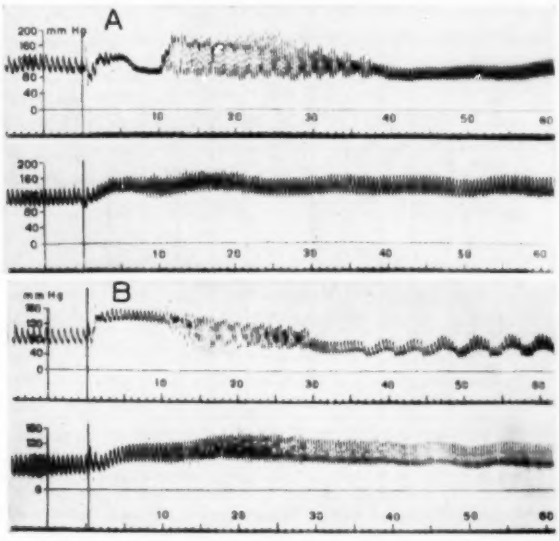

Fig. 1.—*A*, intra-arterial blood pressure in electroshock therapy in the same patient, with and without the administration of a muscle relaxant and oxygen. In the unmodified electroshock (upper curve) the pulsations are seen to cease entirely for four seconds during the tonic phase. The pulse pressure is greatly increased during the clonic phase and fairly low after the end of the convulsion. With the administration of 100 mg. of succinylcholine iodide and oxygen (lower curve) there is only a moderate rise in blood pressure and little change in the pulse pressure.

B, another patient. An abrupt rise in blood pressure occurs in connection with the onset of the tonic phase (upper curve). The variations in pressure after the convulsion are dependent on the deep respiration. With the administration of 100 mg. of succinylcholine iodide and oxygen (lower curve) the rise in blood pressure is less abrupt and more moderate. The respiratory waves are lacking. Time in seconds.

In the case material as a whole, the venous pressure rose by 31.4 mm. Hg without the administration of succinylcholine and by 7.0 mm. Hg when succinylcholine was given. The difference is 24.4 $\pm$ 5.20 mm. and is thus significant ($t = 4.69$; $d.\,f. = 7$; $P < 0.01$).

A rapid and marked increase in the heart rate was observed during the tonic phase of the convulsion in those patients who had not received succinylcholine. The

mean increase in the rate was from 86.1 to 170.6 beats per minute, i. e., an increase of 84.4 beats per minute. With the use of succinylcholine, the mean figure was an increase from 95.1 to 136.1 beats per minute, i. e., an increase of 41.0 beats per minute. The difference between the increases in the pulse rate with and without succinylcholine, respectively, is 43.4 $\pm$ 6.06 beats per minute and is highly significant ($t = 7.16$; $d.\ f. = 6$; $P < 0.001$).

In most cases, both the rate of the heart and the pulse pressure were irregular when strong muscular twitches occurred during the clonic phase, whereas these arrhythmias were almost entirely lacking under the influence of succinylcholine. Despite muscular relaxation, occasional ectopic beats were, however, noted in about one-half the cases. Even with a rapid decrease in the heart rate after the convulsion, no true bradycardia was present; this fact must presumably be ascribed to the premedication with methylscopolamine nitrate.

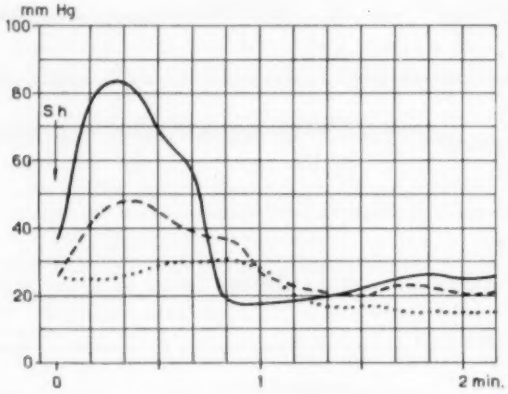

Fig. 2.—The venous pressure in a male patient given electroshock therapy without a muscle relaxant (uppermost curve), with 0.25 mg. of succinylcholine iodide per kilogram of body weight (middle curve) and 100 mg. of succinylcholine iodide (lowest curve), in both cases with oxygen. The rise in venous pressure is almost entirely eliminated by the total muscular relaxation.

COMMENT

We were able to confirm the more or less generally accepted view that a considerable rise in the blood pressure takes place in connection with electroshock, even when a muscle relaxant and oxygen are given. Consequently, the rise in blood pressure must be a centrally conditioned phenomenon and not a product of muscular activity or of asphyxia. It was, however, found that this rise in pressure—which in unmodified electroshock therapy is often sudden and uneven—had a gradual onset and an even course when a muscle relaxant had been administered. The maximal rise in blood pressure was almost significantly lower with the use of a muscle relaxant. Moreover, the otherwise marked variations in the pulse pressure were almost entirely lacking. The relatively low diastolic pressure associated with the strong muscular spasms was presumably due to a decreased return of the blood to the heart. Holmgren and Silfverskiöld [23] have shown that the volume of the heart is decreased during a convulsion produced by electroshock.

The rise in venous pressure, which was often marked in unmodified electroshock, was minimal with satisfactory muscular relaxation; it therefore appears to be mainly a result of the muscular activity. The difference between the rises in venous pressure in the respective cases is significant. Gordh and Silfverskiöld [1] and Silfverskiöld and Åmark [2] found that the rise in venous pressure is a result of increased pressure in the thoracic and abdominal cavities. This rise in pressure in the body cavities can be eliminated by means of muscular relaxation. The inappreciable rise in venous pressure that can still be noted may possibly be ascribed to the rise in the arterial blood pressure.

The increase in the pulse rate when a muscle relaxant had been administered was only half that usually noted, the difference being highly significant. The otherwise common irregularity in the heart rhythm during the clonic phase was lacking. Occasional ectopic beats were, however, recorded even with muscular relaxation. No severe cardiac arrhythmia was present in any case. Methylscopolamine nitrate, a substance with an atropine-like action, was used consistently in our experiments. It presumably had a favorable effect by preventing the vagal reactions which usually occur after the convulsions. The difference observed in the pulse rate may be associated with the elimination of muscular activity, but it may also be dependent on the elimination of asphyxia (Holmberg [24]). The cause of the extrasystoles and of the remaining increase in the pulse rate is probably the same as that of the rise in arterial pressure, i. e., a centrally conditioned stimulation of the sympathetic nervous system.

In electroshock therapy with the usual technique a number of factors place a strain on the circulatory organs. They consist of the muscular strain; asphyxia; a considerable, abrupt, and uneven rise in blood pressure; marked variations in the pulse pressure; an appreciable rise in the venous pressure, and a rapid, irregular heart rate. These are factors which, individually, are possibly of no great consequence during the short time for which the strain lasts, but which, collectively, may not lack importance. It is highly probable that these circulatory disturbances influence the circulation and the gaseous exchange of the brain. It is questionable whether the asphyxia and the circulatory stasis may not actually be the underlying cause of the brain damage that has been observed after electroshock therapy. In electroshock therapy with the administration of succinylcholine and oxygen, these circulatory disturbances are confined to a more moderate rise in the arterial blood pressure and occasional ectopic beats, but to only an inconsiderable rise, or none at all, in the pulse pressure and the venous pressure. Consequently, it should be possible to eliminate to a great extent the risks involved in electroshock therapy by means of the administration of a muscle relaxant and oxygen.

SUMMARY AND CONCLUSIONS

With use of a mechanoelectronic transducer manometer, the intra-arterial pressure was recorded in electroshock therapy with and without succinylcholine iodide as a muscle relaxant. The venous pressure was measured with an aneroid manometer, and the heart rhythm was also recorded.

The arterial blood pressure is found to rise during the electroshock. When the muscular spasms and the asphyxia are eliminated with the administration of succinylcholine and oxygen, a slower and more even rise is noted; the difference

between the maximums with the respective methods is almost significant ($P < 0.05$). The pulse pressure, which undergoes considerable variations with the usual technique, is found to be practically normal when a muscle relaxant is given.

An appreciable rise in the venous pressure takes place in conjunction with unmodified electroshock therapy, whereas only an extremely slight rise is noted under the influence of a muscle relaxant and oxygen. The difference is significant ($P < 0.01$).

In ordinary electroshock therapy the heart rate is found to be irregular and greatly increased. Muscular relaxation produced by succinylcholine is noted to result in a slower and more even rate. The difference between the increases in the heart rate with and without succinylcholine, respectively, is highly significant ($P < 0.001$).

It is concluded that with the use of a muscle relaxant and oxygen it is possible to reduce significantly the strain on the circulatory organs caused by electroshock treatment.

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EEG AND BEHAVIORAL CHANGES ON APPLICATION OF $AL(OH)_3$ CREAM ON PREOCCIPITAL CORTEX OF MONKEYS

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RECENT experimental studies have demonstrated that extensive ablation of the preoccipital cortex in monkeys (Broadmann's Areas 18 and 19) does not affect their visual status (Lashley,[1] Chow,* Riopelle and associates[4]). Animals with such a lesion have normal visual abilities, such as acuity, depth perception, visual field, object recognition, etc., and show good retention of learned visual discriminations. In clinical literature this cortical sector has been considered as a visual integrative center, the damage of which causes severe visual symptoms, notably the various types of visual agnosia (Nielsen[5]). Beside the possibility of a species difference, the discrepancy between animal experimentation and clinical cases may be due to a difference in the nature of brain injury. It has been suggested that pathological brain tissue may create more irritation and disruption of neural functions than the clean removal of that tissue alone (Hebb[6]). In animal work, the ablated prestriate areas are generally resected by subpial suction, a technique which produces minimum scarring, necrosis, and vascular anomalies. Such a lesion may produce little irritation and thus allow the remaining striate cortex to function normally. In human patients, on the other hand, abscess, atrophy, tumor, etc., may invade the preoccipital cortex and constitute a focus of irritation that is responsible for the disruption of visual functions.

The purpose of the present study is to test whether experimentally induced irritative foci situated in the monkey's preoccipital cortex will cause visual dysfunctions that are not obtained by surgical removal of that region. Aluminum hydroxide cream was the agent used to produce pathological lesions. Since the cream has been shown to create chronic epileptogenic centers in the monkey's motor cortex (Kopeloff and associates[7]), it was hoped that a similar effect might also be produced in the prestriate areas. Both electroencephalographic (EEG) recordings and the incidences of convulsive behavior were employed as indices of the irritative effect of the lesion. The monkey's vision was assessed by periodic retention tests of previously learned visual discriminations and by controlled observations on some of the primary visual capacities.

METHODS

Three young adult monkeys (Macacus mulattus) were the subjects of this study. Preoperatively they were trained on three visual discriminations: (*a*) brightness, a lighter gray (53% white, positive) *vs.* a darker gray (25% white); (*b*) color, a red plaque (positive) *vs.* a

From the Yerkes Laboratories of Primate Biology and Moosehaven Research Laboratory.

* References 2 and 3.

green plaque, and (*c*) pattern, a black diamond on a white background (positive) *vs.* black and white horizontal striations. Their visual fields, eye movements, depth perception, and ability to recognize food from inedible objects were also observed under controlled conditions. The general testing procedure, apparatus, and specifications of the stimulus objects are similar to those described in an earlier report (Chow [2]).

After completion of the preoperative training the animals were operated upon under pentobarbital (Nembutal) anesthesia, with aseptic technique. The brain was exposed bilaterally around the posterior parietal region. Silver discs (EEG scalp electrodes) filled with aluminum hydroxide cream were placed on the cortex in front of the lunate sulcus. Two discs were put on each hemisphere of Monkeys 1 and 2. Four discs were applied on the right hemisphere, and five discs on the left, of Monkey 3. The aluminum hydroxide cream (Amphojel) used was obtained commercially. Eighteen months after the first operation Monkey 3 was operated on a second time. The previously imbedded discs were removed; the scar tissues were dissected clean, and four new discs with aluminum hydroxide cream † were applied on each side adjacent to the old placements.

Visual discrimination tests were begun on the first month after operation and were repeated at monthly intervals, with only occasional omissions. These retention tests consisted of 20 trials for each problem. All three problems were presented in one session. The order of giving the discriminations varied from one month to the next.

EEG's were obtained on an eight-channel Grass electroencephalograph. Eight scalp and two ear electrodes were applied, from which both monopolar and bipolar recordings were taken over the major areas of each hemisphere. Recordings were made with the monkey placed either supinely, in a tight wooden box, or pronely, strapped on a board with a head holder. Restraining the animals in this manner for two to three hours before testing had a quieting effect on them. Satisfactory tracings which were relatively free from muscle or movement artifact could thus be obtained without the use of sedatives. Because the records were taken at night, it was possible to get EEG's during natural sleep as well as waking EEG's. The first EEG records were obtained in the fifth postoperative month of Monkeys 1 and 2, and in the third month following the first operation on Monkey 3. Tracings were always taken within a few days following the monthly visual tests.

Several days before the final visual tests and EEG recordings, various amounts of pentylenetetrazol (Metrazol) were given to Monkeys 1 and 2 to induce grand mal convulsions. Monkey 3 developed seizures spontaneously after the second operation. The effects of such preceding grand mal convulsions on visual behavior were observed. In addition, subconvulsive doses of pentylenetetrazol were administered during the final EEG recordings.

After the experiment was completed, the monkeys were killed. Their body weights at the time of death were as follows: Monkey 1 (male), 8.2 kg.; Monkey 2 (female), 6.0 kg.; Monkey 3 (male), 9.7 kg. The brains were fixed and cut into 50 μ coronal sections, and every 10th section was stained with thionine. The locations of the discs were reconstructed from the stained cross sections, and the histological changes of the cortex and the thalamus were examined.

RESULTS

Anatomical Data.—Figure 1 gives the reconstructions of the disc locations, as viewed from the lateral side of the hemispheres of the three monkeys. All the discs with aluminum hydroxide cream were placed on the prestriate cortex in front of the lunate sulcus (Brodmann's Areas 18 and 19), with a few invading the border of the striate area (Area 17). This portion of the prestriate cortex was chosen because of its immediate neighborhood to the striate macular region (Marshall and Talbot [8]). It should be noted that in Monkey 3 the indicated sites include those of both the first and the second operations.

† Dr. N. Kopeloff supplied the aluminum hydroxide cream (#154) used in this second operation.

The discs are entirely encapsulated by a sheath of connective tissue, with some accumulation of blood cells and scarring on their ventral surfaces. The underlying cortex shows clearly the impression of the disc (Fig. 2*A*). As a result, there is a thinning of the cortical layers, accompanied by an increase of glial cells, blood vessels, and nerve cells. Also, there are abnormal neurons (shrunken, poorly stained) and macrophages scattered through the cortex, more concentrated at the upper layers (Fig. 2*B*). In general the anatomical picture of the cortex underlying the individual disc is in agreement with the "meningocortical cicatrix" described by Barrera and associates.[9]

No retrograde degeneration is apparent in the thalamus of Monkey 2. There are small regions of degeneration in the nucleus pulvinaris inferior of the left thalamus in Monkey 1. Small degenerated zones appear bilaterally in the nucleus pulvinaris inferior, the posteroventral part of nucleus pulvinaris lateralis, and the lateral geniculate body in Monkey 3.

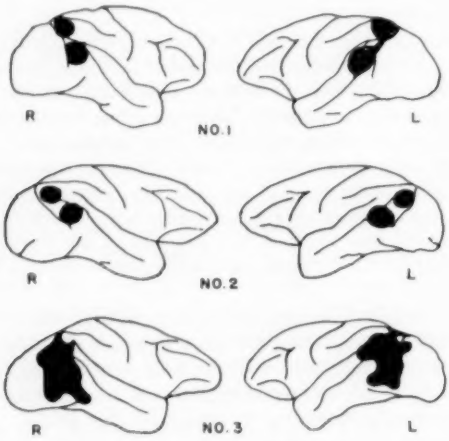

Fig. 1.—Reconstruction of the lateral view of the monkeys' brains. The disc locations of the aluminum hydroxide cream are indicated by solid black. In Monkey 3 the sites include both the first and the second operation.

Electroencephalography.—Records were carefully inspected for the occurrence of epileptic discharges. As a rough measure of the degree of abnormality, a count was made of the number of pages (10-second periods) on which definite spike discharges appeared. The percentage of time that such spike activity was present was then calculated separately for both the sleeping and the waking state of each animal. It should be noted that the wave form and duration of the spikes are such that they often appear similar to the bilateral sharp waves of early sleep which occur over the central regions. Spikes could easily be distinguished, however, on the basis of their unilaterality, focus, and repetitiveness of discharge. Figure 3 is an example of occipital spikes appearing in the same record with sharp sleep waves from the central region. It is interesting to observe that the highest incidence of spike discharges occurs during just this phase of light sleep, when there is evidence of increased synchronization of cortical activity.

Figure 4 shows the EEG findings on the three monkeys plotted against time. Only the percentage of spikes occurring during sleep is indicated. As can be seen, maximum spike discharges were found in Monkey 1 in the 13th postoperative month. At that time two independent foci (one on each side) appeared in the occipital region, with spikes spreading anteriorly to the motor areas. Some spiking was also present during this period in the waking record. After reaching a peak in the 13th postoperative month, the epileptic discharges subsided but were reinstated by the administration of 20 mg. of pentylenetetrazol in the 18th month.

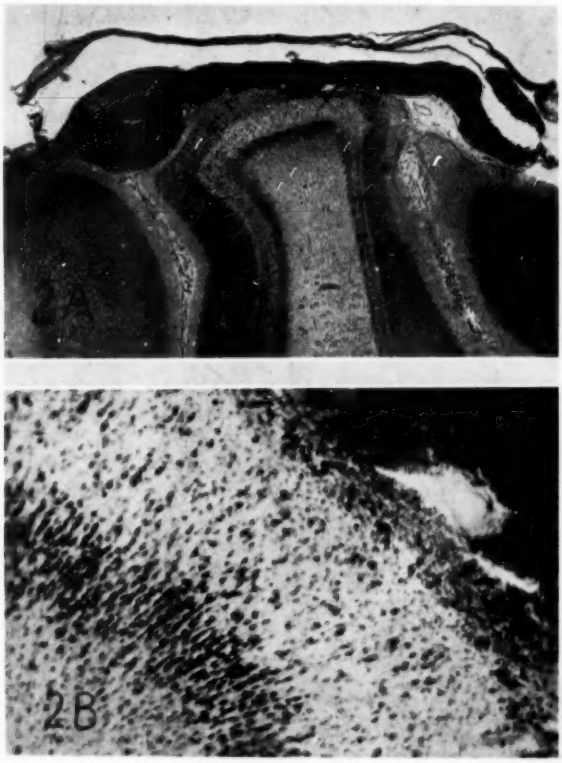

Fig. 2 (Monkey 2).—*A*, low-power photomicrograph, showing an individual disc on the cortex; *B*, higher-power photomicrograph, showing the cortex immediately under the disc (area *X* in *A*). Thionine stain.

Similar findings were obtained on Monkey 2, although the number of epileptic discharges were considerably less. In this case maximum spiking was obtained in the 12th postoperative month from a single focus over the left occipital area. The spikes occurred spontaneously only during sleep. Fifty milligrams of pentylenetetrazol, however, brought out focal spikes during both waking and sleeping states (18th month).

In contrast to Monkeys 1 and 2, Monkey 3 failed to develop any epileptic discharges after the first operation, even after the administration of 40 mg. of pentyl-

enetetrazol. Ten weeks after the second operation spikes were observed during sleep from a single focus in the right posterior parietal area. In the fifth month there were occasional spikes in the waking record, which spread anteriorly to the vicinity of the motor region.

Incidence of Convulsions.—Spontaneous seizures were observed in Monkeys 1 and 3, but not in Monkey 2. Two epileptic episodes occurred in the 13th and 14th postoperative months of Monkey 1, during the period when EEG spike discharges were maximum. The animal was excited on both occasions, i. e., trying to avoid being caught by the experimenter for testing. Convulsive movements followed a sequence, starting with twitching of the facial muscles, then turning of the head

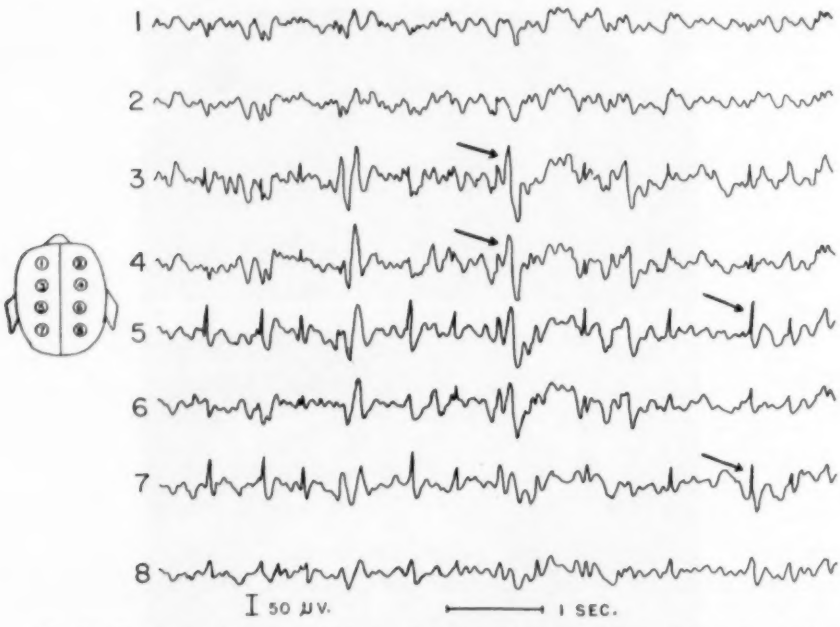

Fig. 3.—Electroencephalogram of Monkey 1, 13 months postoperatively. Monopolar tracings to combined ears, numbered according to the position of the active electrode on the scalp. Upper two arrows point to bilateral sleep waves over the central region. Lower arrows indicate spikes from left parietal and occipital areas.

toward one side, and clonic contractions of the left arm and leg, the seizure lasting about 30 seconds. There was no spread to the other side of the body, and no grand mal seizures resulted.

Five months after the second operation Monkey 3 had a series of grand mal convulsions, each of which displayed the typical tonic, clonic, and coma phases, lasting from one to two minutes. These seizures were observed during various times of the day, even when the animal was not apparently excited. One seizure occurred in the midst of the last EEG recording session, when the monkey was strapped on a board.

Different doses of pentylenetetrazol were needed to induce convulsions in Monkeys 1 and 2. With subcutaneous administration, the former required 40 mg.

of pentylenetetrazol, and the latter, three injections of 40, 60, and 100 mg. of pentylenetetrazol over a one-hour period. The resulting seizures were all typical grand mal with Jacksonian march. They started from the head and spread to the entire body, with clonic and tonic phases, followed by coma and recovery, the seizure lasting from 30 seconds to 1 minute. It is noted that the doses required to produce convulsions are considerably higher than those reported by Johnson and Walker [10] for the intravenous injection of pentylenetetrazol in monkeys with aluminum hydroxide cream applied on the motor cortex.

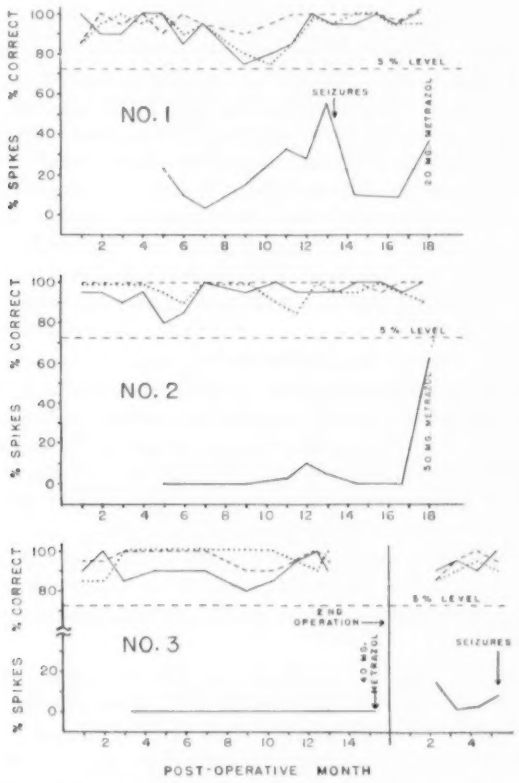

Fig. 4.—Upper curves on each graph indicate the percentages correct on retention tests of three discriminations (solid line, brightness; dashed line, color; dotted line, pattern). All monkeys performed these tests better than chance at the 5% level of confidence. Lower curves indicate the percentages of time during which spikes appeared in the EEG records. The occurrence of spontaneous seizures in two monkeys is indicated by arrows.

Primary Visual Capacities.—There were no detectable disturbances of the primary visual capacities tested (visual field, depth perception, eye movement, and object recognition) in any of the monkeys during any of the monthly observations.

Retention of Visual Discriminations.—All three monkeys learned the three visual discriminations preoperatively within the normal range. Their individual scores will not be listed here. Monthly tests showed almost perfect retention throughout. The

percentages of correct responses are statistically significant at better than the 5% level of confidence for all the serial retention scores by all three animals. They performed the visual discriminations perfectly, even on the second day following the spontaneous or the pentylenetetrazol-induced seizures. Thus, it may be concluded that no detectable dysfunction of visually mediated behavior in monkeys has been demonstrated by the present experiment.

The results of the visual discrimination tests are diagrammatically summarized in Figure 4 along with the EEG findings.

COMMENT

The present series of experiments demonstrate again that local application of aluminum hydroxide cream is effective in producing epileptogenic foci in the monkey's cerebral cortex. The monkeys had both EEG anomalies and epileptic episodes following such treatment. In previous investigations (Kopeloff and associates [7]) the aluminum hydroxide cream has been placed mostly on the monkey's motor area. The present study, extending the earlier findings, shows that such irritative effects may also be induced in cortical areas remote from the motor cortex. The preoccipital region, where the cream is placed in the present study, is not immediately adjacent to the motor area. The occurrence of seizures in these monkeys points to a spread of irritation from the preoccipital region, across some intermediate zones, to the motor area.

On the ability to perform visual tasks these monkeys showed no detectable disturbances during the entire postoperative period. They had perfect retention of learned visual discriminations even when tested the second day following the occurrence of grand mal seizures. Since the irritation spreads to the motor area to cause convulsions, it probably also reaches the nearby striate area. Apparently, the normal functioning of the visual cortex is not disrupted by such spreading effects. The negative finding is at variance with that reported by Pribram.[11] He found that local application of aluminum hydroxide cream in the prefrontal areas caused EEG changes and epileptic seizures. Several days after such seizures there was a temporary impairment of the monkey's performance on delayed response tests and visual discriminations.

The present results may be considered as evidence against the hypothesis, advanced in the introduction, that pathological brain tissue creates more irritation and disruption of neural function than the clean removal of that tissue. Irritative foci experimentally induced in the preoccipital region are as ineffective in producing visual disturbances as the ablation of that region. It is possible, however, that the irritation produced by the aluminum hydroxide cream differs qualitatively from that produced by pathological tissue, i. e., tumor, abscess, atrophy, etc. Thus, although both types of irritation can produce EEG and convulsive changes, only the latter may influence the normal functioning of brain tissue and cause detrimental effects on behavior. Another alternative is that behavioral changes might have been observed if the animals had been tested concurrently with the appearance of EEG spike discharges. Since EEG's were not taken at the actual time of visual testing, there is no way of knowing whether such a possibility could occur. Similarly, the discrepancy between the present negative results on visually mediated behavior and the positive findings reported by Pribram awaits further clarification.

SUMMARY

Three young adult monkeys (Macacus mulattus) were trained on three visual discriminations: brightness, color, and pattern. Their visual fields, eye movements, depth perception, and ability to distinguish food from inedible objects were also observed under standard conditions. After completion of the preoperative testing, two to five silver discs filled with aluminum hydroxide cream were placed aseptically in the preoccipital region in front of the lunate sulcus of both hemispheres. One of the monkeys (Monkey 3) was operated on a second time, when new discs with aluminum hydroxide cream replaced the earlier implanted ones.

Postoperative testing and observations, including EEG recordings, were given at monthly intervals, with only occasional omissions. The following results were obtained: All animals showed abnormal spiking in their EEG records, starting from the 3d to the 11th postoperative months in different subjects. Two monkeys developed spontaneous convulsions, which were observed in the 13th postoperative month (Monkey 1) and in the 5th postoperative month (Monkey 3). All animals showed normal visual status, as well as perfect retention of learned visual discriminations throughout the postoperative period. It is tentatively concluded that local application of aluminum hydroxide cream produces irritative foci in the monkey's preoccipital cortex, but that such irritation does not disrupt the normal functioning of the adjacent prestriate and striate areas to cause any detectable disturbances in visually mediated behavior.

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FURTHER EXPERIENCE IN USE OF THIAMYLAL WITH ELECTROSHOCK

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A PRELIMINARY report of the use of thiamylal (Surital*) sodium with electroshock was first published from the Ypsilanti State Hospital in 1952.[1] Later in the same year Wayne[2] reported the use of thiamylal with electroshock in senile patients. The original report from this hospital included 20 patients who had received electroshock with thiamylal for a total of 94 treatments. It was found that the use of the drug shortened the seizure and prevented any significant rise in blood pressure. In 1953 Green and Leiser[3] published a further report on the subject. Their findings essentially confirmed ours, and, in addition, they noted a prolongation of the postseizure apnea.

Electroshock with thiamylal has been used here for three years on selected patients. No patient has received the thiamylal injection without indication, as it has been our feeling that the use of any drug with electroshock adds some danger. We have, however, felt that the added risk is extremely minimal. By Nov. 1, 1953, a series of 77 patients had received a total of 1,007 electroshocks with thiamylal. The group included 40 males and 37 females.

Thiamylal is an ultra-short-acting thiobarbiturate. We have been administering it intravenously in a 2.5% solution. The drug has been used extensively in anesthesia,† with satisfactory results, and complications resulting from its use have been few. It is also useful as a narcoanalysant.[6] Laryngospasm is rare and has never been encountered in our series. An occasional patient will hiccough after the electroshock has been given. If this does occur, it is apt to recur repeatedly in the same patient. This has never been a serious complication and has never warranted discontinuing the treatment. We always turn the patient onto his side after cessation of the convulsion, and if respirations are slow diaphragmatic pressure for a short time will usually solve the problem. An occasional patient will vomit after treatment. The incidence is much higher if the patient has accidentally received breakfast before treatment.

Green and Leiser stressed the prolongation of postseizure apnea. They also noted that "the total period of apnea tends to remain constant in treatment both with and without thiamylal." We have not been impressed by apnea but have noted a relatively high incidence of shallow respirations. Those patients who require a greater amount of the drug appear to be more prone to shallow breathing or a period of apnea. We have given up to 1 gm. of thiamylal without complication

From the Ypsilanti State Hospital.

* Parke, Davis & Company trademark for the sodium salt of 5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid.

† References 4 and 5.

except for delayed waking. Most patients, however, require less than 0.5 gm., and our normal procedure is to use a 20 cc. syringe containing 0.5 gm. (20 cc.) and to inject the required amount. We have no evidence that a patient develops tolerance to the drug during a course of treatment. The toxicity of the drug also appears to be minimal.[7]

The uses for electroshock with thiamylal have increased as we have become more familiar with the treatment. In our original paper we noted that muscular activity was abolished or so minimized that the treatment was safe for patients with fractures or other bony lesions. The rise in blood pressure and in pulse rate was also significantly less, making it safer for patients with a questionable cardiovascular status. It is important that the seizure be abolished in patients with bony lesions. To assure this result, we give sufficient drug to abolish the corneal reflex and relax the patient. However, pulse and blood pressure rises are prevented if the narcosis is sufficiently deep to abolish only the lid reflex. This depth may or may not prevent a seizure. In a typical thiamylal-shock seizure there are movement of the lids, facial twitches, and occasional upward rolling of the eyes, without contraction of the muscles of the extremities or spine. We are in the habit of

TABLE 1.—*Indications for Thiamylal with Electroshock*

Bony lesion	17
Anxiety	28
Recent postoperative	3
Cardiovascular	12
Thrombophlebitis	2
General debility	8
Postshock excitement	6
Disturbed	4
Tuberculosis	1
Hernia	2

recording these as grand mal seizures on the treatment record in order that the number of therapeutic treatments will be correct. Actually, however, there is no grand mal reaction. The response is better described as an atypical petit mal seizure.

As previously indicated, no patient received the thiamylal injection without an indication. Also, we have encountered no contraindications except in patients with veins nearly impossible to inject. Table 1 shows the types of indications and their occurrence. Several patients had more than one reason for receiving thiamylal, and several patients received more than one course of electroshock with thiamylal. We have also been using the drug with increasing frequency in those patients who are apprehensive regarding electroshock.

Bony lesions included various types of fractures, osteoarthritis, and, in two patients, osteoporosis. General debility included old age or generally poor health. The drug was found especially useful for patients who experienced postelectroshock excitement. Inasmuch as the waking period after treatment was delayed to 15 minutes instead of the usual 5 minutes, the patients were asleep during the most excitable period. (Green and Leiser [3] reported thiamylal delay as 11.7 minutes.) Three patients in our series were given thiamylal because of disturbance. These were seclusion patients who were extremely combative, and frequently the injection was given in the seclusion room.

One patient in the series died on the electroshock table at his second treatment. This case was a calculated risk, the patient having a known acute abdominal condition at electroshock. He was a 27-year-old Negro in a catatonic stupor, a recent postoperative case, and so severely negativistic that the department of surgery elected to delay further operation until his mental condition improved. At autopsy he was found to have extensive gangrene of the jejunum, a lesion which was probably inoperable.

All patients received the electroshock according to the usual indications. Other forms of therapy were used in conjunction with the shock as seemed indicated, such as occupational therapy, recreational therapy, and psychotherapy. No attempt is being made to credit the patient's recovery to shock with thiamylal per se. Inasmuch as thiamylal was administered as indication dictated, the group is a heterogeneous one and includes patients with both good and poor prognoses, complicated by physical handicaps or older age. Eighteen, or 23%, of the group were 60 years old or over. This group also included many patients categorized as having chronic schizophrenia who adjust better in the hospital if they receive maintenance electroshock and who have been ill for many years. Forty-three, or 55%, of the

TABLE 2.—*Results of Treatment with Thiamylal*

	Male	Female
No. in group	40	37
Previous EST	22	21
Improved	18	13
Complete thiamylal course	13	12
Temporarily improved	14	10
Complete thiamylal course	10	8
No improvement	8	14
Complete thiamylal course	3	9

total group had had previous courses of standard electroshock treatment. Because thiamylal has been used almost exclusively for patients with the aforementioned indications, we have no comparable series of patients who received standard electroshock.

Fifty-five patients in the series had complete thiamylal courses. Twenty-two either were started on standard electroshock and finished the course with thiamylal, or were started on thiamylal and completed the course with standard electroshock—depending on the indications that existed at the moment. With those who experienced postelectroshock excitement, therapy was started on standard shock and changed to thiamylal shock because of the excitement. After improvement had occurred, it was often possible to give further standard treatment without recurrence of the excitement.

Thirty-one, or 42%, of the group were considered improved, either in hospital adjustment or by release to home. Of these, 25 had had complete thiamylal courses, and 6 had had mixed treatment. Twenty-four, or 31%, showed temporary improvement, or improvement which lasted less than six months. Eighteen of these had had complete thiamylal courses. Twenty-two, or 28%, of the group showed no improvement or no immediate improvement. Thirteen of these 22 had had previous electroshock, and 12 had had complete thiamylal courses.

COMMENT

It is difficult to evaluate the relative therapeutic efficacy of electroshock with thiamylal as compared with conventional electroshock. It is our impression that psychiatric improvement occurs with the same frequency, whether given with or without thiamylal. Thiamylal, however, enables some patients to receive treatment who would otherwise be excluded. In some patients the anxiety regarding electroshock was so acute as to constitute a questionable contraindication. Electroshock with thiamylal appears admirably suited to this type of patient. Unfortunately, our series is not satisfactory for an accurate evaluation of the results when the anxiety factor has been removed by the drug. Twenty-one of the 28 patients who received thiamylal with electroshock for anxiety had had previous electroshock and appeared chronic. The lack of complications and the satisfactory results of electroshock with thiamylal lead us to believe that this modification of electroshock therapy has a definite place in the treatment of mental disorders complicated by physical disease or by anxiety regarding the treatment. An additional study is being made at this time regarding the electroencephalographic changes during electroshock with thiamylal and will be prepared for publication.

SUMMARY AND CONCLUSIONS

Seventy-seven patients have received 1,007 electroshocks in conjunction with thiamylal.

One fatality is reported in which the patient had physical complications severe enough in themselves to cause death.

Electroshock in conjunction with thiamylal is safe, when properly administered, for patients with bony lesions. It is safer than standard electroshock for those with cardiovascular disorders and useful for patients with anxiety regarding the treatment.

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APPETITIVE BEHAVIOR AND SIGN STIMULI IN HUMAN LIFE

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SOME HUMAN behavioral disturbances may be given a biological and uniform type of interpretation; it requires a new usage of some old evolutionary and neurological ideas and the employment of some new biological observations and hypotheses.[1]

First, behavior is seen as the direct outcome of the evolutionary struggle for existence, as being basically the expression of the factors which made survival of that struggle possible.

Customarily, man's relation to the rest of the animal group is not regarded as a primary, dynamic force underlying his behavior. It is seen as something the human organism tries to get away from; the animal components of man must be repressed and escaped from for man to fit into society. Instincts, when regarded at all as inherited, evolutionary qualities, are considered more as nuisances than as essential parts of man and as the intrinsic foundation of his individual and social behavior. Many types of instinctive behavior are deemed destructive and their quelling constructive, or "anagogic" and "katagogic" (Stekel). These evaluations of instincts seem made solely from the standpoint of social organization; they do not seem to consider the huge component of the human personality comprised by instincts or the integral part of civilization they actually are.

DEFINITIONS

The discussion must be preceded by a summarized review of the subject of the telencephalization of survival functions.

Survival Functions.—These are functions, characteristic of a species or larger group, which help it to survive in the evolutionary struggle for existence.*

Some functions that may be considered important in surviving the struggle for existence are as follows:

1. *Primary Survival Functions Relating to the Self.*—(A) Behavior of the individual as an entity. Long before there is any detectable apparatus by which an organism can consciously identify itself as an individual entity, it nonetheless behaves as one; ultimately forms evolve in which the individual can consciously identify himself as a self, distinct and separate from everything else in the universe. Even plants react as individual entities, separate from all other entities, as when they choke off each other's roots, or when a root grows around a rock. The suggestion is that this process, when operated by a cerebral cortex, becomes the basis of individuality and personal identification. (B) The self-evident necessity or importance with which

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From the Neurological Service of Mount Sinai Hospital, Dr. Morris Bender, Chief Neurologist.

* References 2 and 3.

each organism satisfies such needs as eating and mating. It is suggested that as this feeling of importance becomes corticated, and more and more elaborated, there develops a recognition of the importance of the whole self (human ego importance).

These two survival functions serve as a foundation for all the others, which could not be properly manifested without them. An organism could not react to its own hunger without the first; it would not be driven to seek prey without the second.

In human beings we see these two functions, heavily corticated, manifested incessantly, from the care of his life a man takes in crossing the street, through the quest for at least a modicum of prestige, to the pursuit of great power.

2. *Ways of Responding to Other Individual Entities.*—(A) Hostile: (*a*) in rage; (*b*) by attack, as in killing prey. (B) Reactions to hostility: (*a*) in fear; (*b*) by defense. (C) Nonhostile—perhaps friendly: (*a*) having harmonious relations as in grooming and in actual physical union by mating; (*b*) caring for the young by parents; (*c*) by being dependent upon parents while still young and helpless; (*d*) by gregariousness, which may be dependence upon presence in a group for actual survival, i. e., ants, schools of fish, flocks of birds, and human groups.[2]

These phenomena, when they appear in human behavior, are usually not recognized as being present only because of their evolutionary survival value. The processes underlying evolutionary survival as manifested through the human brain are the roots of man's behavior. Society is the expression of those functions.

The Cortex in Survival.—Man's body lacks most of the special adaptations possessed by our predecessors, like the elephant's weight, the tiger's strength, the falcon's diving speed. The survival functions have to be manifested otherwise.

The cortex probably enabled our bodies to compensate for what they lacked since our beginnings; by now it has given us the equivalent or better of probably every special adaptation possessed by any creature. . . . The facilities . . . made possible by the human cortex are unprecedented for elaborateness. They would necessarily be elaborate, if we are to attribute any evolutionary significance to the human cortex. . . . To our cortex must be attributed our capacity to survive the (evolutionary) struggle for existence, not only in primitive times but also now, for the environment—especially that part of it that is human—is still threatening, and the Darwinian struggle still great. . . .[2]

Telencephalization of Survival Functions.—The human brain takes over and dominates and elaborates the expression of survival functions by telencephalization.

Encephalization and Telencephalization.—Encephalization is the name for the biological process by which each newly evolved cephalad addition to the brain becomes inextricably involved in, complicates, and dominates the performance of all old parts and functions. The concept of encephalization is an old one, dealt with by many students of neurology.

With the appearance of recognizable new parts of the brain, we speak of metencephalization, mesencephalization, diencephalization and finally, in reference to the forebrain, telencephalization.

When ventral fins become the legs of amphibians, for instance, increased mesencephalization multiplies the functions of the extremities greatly beyond their limits in fishes. But this advance in complexity is minute compared to the multiplications produced by the human telencephalon by which, for example, walking may become a tool for exploring African jungles, vocal sounds become language, and vision the reading of meanings in the form of words.

The concept of mesencephalization, telencephalization, etc., has always been applied to isolated acts like the use of the limbs. The present and new purpose is to extend it and apply it to the whole systems of parts involved in carrying out such functions as rage, defense, dependence, and the other survival functions. Limb use, for example, is only one small part of the machinery of rage; among the many other parts involved are the parts of the brain pointed to by Bard.[2]

The cortex is, thus, not an organ for repressing primitive processes in the interests of group living; one of its main functions is the expression of these very processes, or survival functions. There is nothing to suggest a change in these functions, or in the evolutionary functions of the brain, as the result of the gathering of humans into societies. In fact, this very gathering is, itself, a survival function (*2 C d*, above). Various cultures differ in the ways they teach of telencephalizing survival functions. Through this teaching the survival functions become telencephalized in civilized form. A function of civilization is that of permitting, facilitating, and even forcing the manifestation of these functions, which are part of the human constitution.

What may look like suppression of a survival function in a society is likely to be merely the suppression of certain ways of expressing it. Certain other ways of expressing it are not suppressed but even demanded. Accordingly, expression of the survival functions is expected, but only according to methods prescribed by cultural dictate. An example is that of attacking and killing in war, in which individual participation is not only expected but demanded.

The differences between inherited and acquired encephalizations have been discussed elsewhere.[2] Here it is sufficient to say that an acquired telencephalization is a learned way of dealing with a survival function.

Instinct.—Tinbergen,[1] who has contributed greatly to the study of instinct, has summarized his own studies and hypotheses and those of Lorenz and other biologists in a book which should be very useful and provocative to those interested in the biology, neurology, psychology, and psychiatry of human behavior, although Tinbergen himself scarcely touches directly upon the behavior of man.

He tentatively defines "an instinct as a hierarchically organized nervous mechanism which is susceptible to certain priming, releasing and directive impulses of internal as well as external origin, and which responds to these impulses by coordinated movements that contribute to the maintenance of the individual and the species." †

Sign Stimuli.—Tinbergen says:

> As a rule, an instinctive reaction responds to only a very few stimuli, and the greater part of the environment has little or no influence, even though the animal may have the sensory equipment for receiving numerous details.
>
> For instance, the spring fighting of male sticklebacks . . . is especially directed against other male sticklebacks in nuptial markings. As the males differ from other animals, especially in having an intensely red throat and belly, it seems probable that the red colour might be the most important stimulus. This has been tested in the following way. Models of sticklebacks were presented to a number of males. Some of the models were very crude imitations of sticklebacks, lacking many of the characteristics of the species or even of fish in general, but possessing a red belly. Others were accurate imitations of sticklebacks, but lacked the red. The males attacked the first group of models much more vigorously than they did the others. In this experiment the red colour was put into competition against all other morphological characters together. The results prove that the fish reacted essentially to the red and neglected the other characteristics. Yet its eyes are perfectly able to "see" these other details.‡

Russell has named these essential stimuli "sign stimuli," [4] and Tinbergen and others employ the term.

† Tinbergen,[1] p. 112.

‡ Tinbergen,[1] pp. 27 and 28.

Innate Releasing Mechanism.—Tinbergen stated:

The strict dependence of an innate reaction on a certain set of sign stimuli leads to the conclusion that there must be a special neurosensory mechanism that releases the reaction and is responsible for its selective susceptibility to such a very special combination of sign stimuli. This mechanism we will call the Innate Releasing Mechanism (IRM), a free translation of the German term *das angeborene auslösende Schema* (von Uexküll-Lorenz).§

I. R. M.'s in organisms like the fish are, of course, inherited. In highly corticated organisms like man they are inherited, too; in addition, new ones are gained by learning. Thus, man can learn to respond to new sign stimuli. He can also learn to produce new sign stimuli for others to respond to. These new I. R. M.'s and new sign stimuli are telencephalic products and are telencephalizations of instincts.

Instincts and Survival Functions.—In one sense, the two terms refer to the same thing. They are both employed, however, because they have somewhat different uses. Survival function is a more inclusive term than instinct; one survival function, like infantile dependence, employs numerous instincts. The telencephalization of the apparatus of a survival function is, therefore, telencephalization of the apparatus of an instinct or group of instincts.

Appetitive Behavior and Consummatory Act.—Craig described these two phases of instinctive behavior.[5] The consummatory act is usually "the end of a bout of prolonged activity" ‖; evidently "it satisfies the animal." Such acts as fighting, "playing the broken wing," eating, and coition are given as examples.

Craig "called the introductory striving or searching phase 'appetitive behaviour' to stress the fact that the animal is striving to attain some end" (Tinbergen¶). Tinbergen goes on to a type of movement often called "random movement," "exploratory behaviour," "seeking behaviour," or the like. Contrary to the consummatory action it is not characterized by a stereotyped motor pattern, but rather by (1) its variability and plasticity and (2) its purposiveness. The animal in which a major drive, like the hunting drive, the nest-building drive, the mating drive, is activated starts searching or exploratory excursions which last until a situation is found which provides the animal with the stimuli adequate for releasing the consummatory act.

Appetitive behavior may be a very simple introduction to a consummatory action, as in the case of a frog catching a prey; the preparatory taxis (turning toward the prey) is true purposive behaviour, and is continued or repeated until the prey is within range and in the median plane.¶

Discussing this matter further, Tinbergen says:

A consideration of the relationships between appetitive behaviour and consummatory act is important for our understanding of the nature of striving in animals. It is often stressed that animals are striving towards the attainment of a certain end or goal.

Lorenz has pointed out not only that purposiveness, the striving towards an end, is typical only of appetitive behaviour and not of consummatory actions, but also that the end of purposive behaviour is not the attainment of an object or a situation itself, but the performance of the consummatory action, which is attained as a consequence of the animal's arrival at an external situation which provides the special sign stimuli releasing the consummatory act. Even

§ Tinbergen,[1] pp. 41-42.

‖ Tinbergen,[1] p. 104.

¶ Tinbergen,[1] p. 105.

psychologists who have watched hundreds of rats running a maze rarely realize that, strictly speaking, it is not the litter or the food the animal is striving towards, but the performance itself of the maternal activities or eating.#

APPETITIVE SEARCHES AND SIGN STIMULI

The biologist's descriptions of appetitive searches for effective sign stimuli to consummate instincts (or, more broadly, survival functions, according to the present theme) furnish a new light in which to examine human behavior. Even superficial consideration does seem to justify the idea that our own behavior contains such elements.

More thorough study suggests that some important phases of human activity not only contain these elements but actually consist of such appetitive searches for certain sign stimuli. In such situations the appetitive search itself thus becomes of key importance.

Examples are people who fail to develop any real interest in their professions, whose interest is said to be only "skin deep." The situation might be explained by the idea that nothing is of real interest to any human except instinct. Those who have been satisfied with their professions have found it an adequate telencephalization of certain instincts or survival functions; the energy entering the appetitive search for the appropriate learned sign stimuli for activating that instinct or survival function is the very energy that is applied to the profession. The instincts mainly involved may be those related mainly to the self. This is, of course, related to the process called sublimation, in a psychological sense. However, "sublimation" represents a fortunate mode of siphoning off an instinct which might otherwise have been destructive. The telencephalization idea, on the other hand, means that the individual was fortunate in being able to find an instinct he could transmute into a profession; thus he gained the chance for an active, interesting, and very probably useful career.

When a person fails to find satisfaction in his profession or other work, it may be because the work involved has no direct appetitive meaning to him. Certain pathological states will be discussed later which suggest that, with little or no instinctive activation at all, people feel "unalive," depersonalized, without meaning.

It is certainly conceivable that many careers are really nothing other than appetitive searches for complex learned sign stimuli. Sometimes these searches may take very direct forms, as in the case of a certain gynecological resident, who was ardent about examining and douching patients' vaginas.

The phenomenon of dependence may also manifest itself appetitively, for example, in the well-known situation of a man who can function adequately as second in command, but not at all at the top, because of a need to have someone above him to lean on. Much of the activity of such people may be the appetitive search for an appropriate sign stimulus to consummate the dependent behavior.

Careers may be based on rage and attack. A profession may be selected because it offers opportunities for sign stimuli for consummating rage and attack.

In the name of public weal sign stimuli are sought. "Punishment" is vented, and the attack function is consummated, while the attacker gains social sanction for his actions. The sign stimuli are people; often they are social offenders, inimical to the welfare of the community, although sometimes they are merely types in dis-

Tinbergen,[1] p. 106.

favor; actually it makes no difference which they are, for they serve the appetites of the attackers equally well. In such cases as the New England witch trials as they are described, the impression is gained that the prosecutors were engaged in an appetitive search for sign stimuli to consummate their attack and rage functions rather than a drive for social good, despite the disguise of social welfare even in their own minds. Thus the appetitive needs of an individual may became a substitute for the good of the community, and the appetitive search may replace judgment. In such instances any benefit to the community is incidental and is unlikely to outweigh the harm done by institutionalizing an aggressive appetitive search pursued without insight.

In many instances the power an employer has over his employees aids him in using the employees as sign stimuli for rage. People may even seek power so as to gain the chance to use as sign stimuli a ready-made group of victims. It should be no surprise that such employers are the ones who complained the most when they were in the position of sign stimuli.

Certain types of childhood repression of rage and attack (below) may even color the general behavior of a whole culture. It was thought by Dicks * and others that a typical German cultural trait, during and long before Hitler, was just this type of repression of rage and attack against fathers, and that other targets (Jews, Catholics, and other minorities) were readily accepted if sanctioned by father figures. From the present point of view these targets would not only be accepted, they would be appetitively sought as sign stimuli.

The culturally induced repression of rage against the father does not mean repression of the rage and attack functions altogether; it merely indicates one way in which they are not to be expressed. The attacks on the minorities represented a way in which the culture, at least at the time, did expect, and even demand, that its members manifest these survival functions.

Ordinary states of acute or recurring rage also need consummation. Often the appetitive search for a sign stimulus to consummate the function is shown by the effort to pick a fight. The enraged person is "spoiling for a fight." The sought victim is the sign stimulus. The characteristics a victim must have in order to serve as an adequate sign stimulus vary from culture to culture and to some extent from family to family; these variations cannot be described here.

Sometimes alcohol is needed to enable the individual to undertake the appetitive pursuit; learned sign stimuli for fear are, supposedly, temporarily laid away by it. The pressure of the functions of rage and attack may be measured in a way by the considerable amount of time and energy the person will devote to preparing himself and seeking and finding the sign stimulus. Evidently the pressure of these functions may be as great as that of sex.

Many people have special sign stimuli serving for rage consummation, such as, for example, telephone operators who are never seen. Irate people sometimes become embroiled with a telephone operator for purposes of consummation.

Thorne, in his paper concerning frustration-anger-hostility states, mentions the triggering off of large quantities of repressed anger by inconsequential neural

* Dicks, H.: Personal communication to the author.

stimuli.[6] From the present point of view, these inconsequential stimuli may belong to the general class of learned sign stimuli and may be actively sought for in an appetitive way.

Thorne also describes a tendency of "anger reactions to radiate or generalize with the development of an increasing range of excitants." The lead is taken from the idea of Cameron and Cameron[7] of the generalization of anxiety reactions.†

SOME DISTURBED STATES SEEN IN TERMS OF APPETITIVE SEARCHES AND SIGN STIMULI

Some common syndromes of disturbed or psychoneurotic behavior also appear to be constructed mainly out of appetitive searches, repeated again and again as the instinctive need recurs and recurs.

The clinical conditions are too familiar to need detailed description; they will be described in terms of the concepts under discussion—but only briefly, and necessarily in an oversimplified manner.

Later, actual evidence which is at least compatible with these concepts will be given.

A realistic possibility is that such a thing as instinct, or survival function, "imbalance" exists. It might possibly arise from early habitual frustration of that function. All of life could be devoted to a fruitless search for consummation, and that single instinct or survival function could be the single dominant dynamic factor in a person's whole behavior, with the others greatly reduced. A "well-balanced," highly judicial person may be some one of whom this only slightly true. When it is true, large amounts of energy will be concentrated around that one instinct or instinct group; after consummation there is little for the individual to do but seek early repetition, having virtually no other great need to turn to.

The radiation tendency of reactions referred to above and considered appetitive from the present standpoint may aid in making an instinct or survival function predominant.

These hypotheses appear to have the following advantages: 1. They may approximate the actual truth. 2. They provide a regular biological rank for a number of disturbances conventionally classified according to psychological rather than biological systems, with roots pictured as lying only in other psychological systems. 3. Conventionally, the deviant or pathological aspects of the disturbance are not seen themselves as representing any regular, normal biological activity; according

† Rage, rather than anger, and fear, rather than anxiety, would be the terms of choice from the viewpoint of survival functions, anger and anxiety being the telencephalizations of the more basic survival functions.

Various other social, political, economic, and other attitudes may also really be little but appetitive searches. The attitude of some people toward crime is merely to punish the offender rather than studiously to find a cause and prevent it. Some like to defend underdogs "to my last drop of blood," and the likelihood is that the defending rather than the underdog is the important point. Teen-age glandular excitement, combined with a first look at the nature of man and his environment, often leads to wild excesses of attack in the name of "justice," with a passionate search for victims; the outcome can be zealous adherence to a political party, and this can just as readily be the Republican Party as a radical one.

to this view, they do. 4. The hypotheses make possible a reclassification of various conditions which clinically seem divergent, but which are dynamically closely related when seen from the present viewpoint. 5. They suggest a direct therapeutic approach.

1. *Cases in Which an Aberrant Learned Sign Stimulus Is Itself of Major Importance.*—Every instinct must have sign stimuli to trigger its I. R. M.; humans must inherit I. R. M.'s for responding to uniform human sign stimuli. In addition, they acquire the capacity to respond to new sign stimuli, and this is done by telencephalic learning.‡ The new, learned I. R. M.'s dominate the entire execution of the instinct (or survival function). Thus, the instinct, or survival function, has become telencephalized; this is meant as literally in a neural, or structural, sense as is mesencephalization of limb movements, or the telencephalization of foot movements in the chimpanzee.[8]

Ordinarily, learned sign stimuli may be supposed to coincide with and reinforce the inherited ones (male sexual stimulation by female blonde hair, various types of female figure, etc.) or to repress them, serving a biological function in either case. However, in the type of case to be alluded to they operate by replacing the inherited sign stimuli; thus, they give the survival function distorted expression, with no evident biological function.

A. Fetishism: In the case of a fetishist whose neural sexual apparatus can be triggered only by looking at or touching a black silk stocking, the stocking is a sign stimulus.

This learned sign stimulus has superseded the inherited ones; the inherited sign stimuli are ineffective to release the sexual machinery in such a case. The sign stimuli which activate the sexual machinery in most males do not do so in this one; nevertheless, we must assume that the individual has inherited the same basic sign stimuli as other males. But the inherited sign stimuli have been capped over, hidden, and rendered difficult or impossible to activate by unusual learned sign stimuli.

The patient will then search "obsessively" for a stocking when he is sexually activated by, for example, glandular stimuli. At least we call the search "obsessive," but it enhances our comprehension if we drop that term and instead regard the behavior as the appetitive pursuit of a learned sign stimulus by which the sexual instinct can be consummated. The enormous energy, the unremitting drive which goes into that "obsessive" search, is the same drive as that employed in the search for ordinary inherited sexual sign stimuli in other males, and should therefore not be regarded either as obsessive or as pathological in itself. A fetishist, in searching for the learned sign stimulus, may indeed expend more energy than would normal males, but this perhaps results from "instinct imbalance" (above), or possibly also insufficiency of satisfaction of the instinctive need, when the consummation is achieved by such basically inadequate sign stimuli as stockings.

‡ The question may well be raised whether sign stimuli, or I. R. M.'s, or both are the new thing which is learned. There is no way to be sure at this point. However, if the hypothesis has any reality at all, then visibly new sign stimuli are learned, as will be shown below. These new sign stimuli may activate old, inherited I. R. M.'s or may require new, learned I. R. M.'s to act upon. Information on this point is, of course, lacking. But since we are on secure ground in speaking of learned sign stimuli (granted the validity of the hypothesis at all), this is the term that will be employed; we shall refer to learned sign stimuli and not learned I. R. M.'s.

The searching behavior is probably not the same as many types of true obsessive or compulsive acts, such as touching fence posts, needing to repeat acts a certain number of times, etc. The term "obsessive," as we usually use it, covers many different types of behavior, which probably ought to be considered under separate headings.

This interpretation of fetishism gives it, as well as its apparent abnormality, rank among the phenomena of biology and makes it unnecessary to view it as a sport, or as a human pathological phenomenon unrelated to the rest of nature in any fundamental way.

Also, the "obsessive" aspect does not appear among the abnormal phases of the condition, requiring psychopathological explanation.

B. Homosexuality: Some types of homosexuality may perhaps be classified in the same category as the type of fetishism mentioned above, as, for example, when the genitalia of another male constitute the learned sign stimulus; those genitalia have to be seen or touched for sexual consummation to be reached. The genitalia of the other male are, indeed, a kind of fetish in themselves under these conditions. Some patients even obtain consummation merely by the touching of their penis to the penis of another male.

In ordinary psychodynamic thinking, acts like these are deemed "symbolic sexual acts," the penis of the sexual partner being the major symbol. The probable truth of this, from a psychological standpoint, does not negate the more fundamental biological explanation now being attempted; according to this explanation, the partner's penis constitutes a learned sign stimulus which has superseded the inherited ones, and which must be appetitively sought in order to permit sexual consummation.

2. *Cases with Appetitive Searches for Nonaberrant Sign Stimuli.*—A. Infantile Overdependence: In another common type of case, exemplified by adults who retain a high state of infantile overdependence, the relation of the sign stimulus to the behavior disturbance differs from that first discussed in at least the following ways:

(*a*) The appetitive search may be just as relentless and persistent as the pursuit of a stocking by a fetishist. However, the importance of the specific sign stimulus itself seems to be different; with the fetishist, the specific sign stimulus as such appears almost as important as the instinct it operates. Also, the sign stimulus is not so narrowly defined as to be virtually limited to one object. While a parent is the major sign stimulus, he or she can be substituted for, and parent figures of many varieties are, of course, common. Hence the instincts comprising the survival function of infantile dependence in these cases can respond to a wider variety of sign stimuli than the sex instinct in the types of case referred to above.

(*b*) The sign stimulus is of the type which does coincide with and reinforce the inherited ones. Infants inherit the I. R. M. to respond to mothers, but to identify his own individual mother each infant must do telencephalic learning. By means of this process he gains his own mother as his own major learned sign stimulus.

(*c*) The role of the sign stimulus becomes very complex. The same sign stimulus appears to activate the machinery for more than one survival function, e. g., fear and dependence. The patient may retain a high level of infantile dependence so as

to have protection against something he fears, and he may appetitively seek a parent as the sign stimulus to operate the survival function of dependence. At the same time, his predominant fears may center around that very parent or perhaps his other parent. Whichever the main precipitants of fear are, one sign stimulus (or two closely related ones, e. g., a mother and a father) is likely to activate more than one survival function. The habitual simultaneous activation of fear and dependence under these conditions can constitute a frustrating cycle of events; and the gaining of adult stature, with ability to function responsibly and independently in society, is retarded.

Rage and attack may also be woven into this complex picture of dependence. A child with rage against a parent may completely repress it and also fear its hidden presence to an extent sufficiently great to elicit all the fear just described. Then the rage may help perpetuate the state of infantile dependence under discussion.

The behavior of such an individual may also be lived out in the form of a career, political or otherwise, as was indicated above.

B. Care of Young: The extreme example of an appetitive search for a sign stimulus would perhaps be that of a woman who kidnaps a baby in order to care for it.

Instances are many, however, in which adults seek young to care for in acceptable and useful ways, making a career of the activity. Perhaps the classifying of these cases is a matter of which behavioral school the classifier comes from; some consider this type of drive psychoneurotic, because it needs continual resatisfying in a recurrent way; others do not consider it so, because the fulfilling of the individual's need coincides with a societal need.

We do see the survival function sometimes exaggerated to a degree at which its consummation becomes an insupportable burden for the young upon whom the function is vented.

It may seem surprising to find the next groups classified here. But, according to the basis of classification employed, there are dynamic reasons for listing these, and perhaps some other clinical groups, under one heading.

C. Hypochondriasis: The main survival functions involved are those described as behavior-as-an-individual entity and the importance-of-satisfying-the-needs-of-the-organism, as well as dependence. The physical symptoms serve as sign stimuli by which these functions may be consummated in terms of the receipt of importance, love, and care.

D. Paranoid Reactions: Thorne postulates that "chronic anger reactions create states of aggressiveness in which the underlying hostile feelings and emotions dominate the psychic field or stimulate distortions of perception, thinking, reality testing and identification with other people." He suggests that the underlying state of chronic anger explains most of the clinical observations which have been made concerning paranoid behavior.[6]

Thorne's ideas seem related to those developed here. The chronic anger would inescapably lead to an appetitive search for consummative sign stimuli, and these would be the victims (sometimes "paranees" [9]). The plot, including the retrospective falsification, could easily arise from the search, even being part of it.

3. Development of Unusual Sign Stimuli for Manifesting Survival Functions Whose Regular Modes of Operation Have Been Lost.—A. Some Cases of Schizophrenia with Somatic Delusions: The cases to be considered are certain instances of schizophrenia with somatic delusions.

An 18-year-old youth, who exemplifies the kind of case under consideration, had the acute onset of delusions of falling, deformed, discolored hair. He was severely depressed and in terror and required hospitalization. He was "obsessed" with his hair symptoms and could think and talk of little else.

In fact, he seemed to have no other life except his hair. Survival functions were scarcely manifested, except as expressed through his hair symptoms. Fear was so expressed, intensely. Rage at the physician was often shown if the latter failed to understand something about the hair. Interrelationship with others (the gregarious type of dependence) was limited to the physician, and this interrelationship was carried on solely through the currency of the hair.

By the hypotheses now employed, such a situation might be understood as fundamentally a loss of the capacity of all the patient's sign stimuli to operate his instincts. This would mean that few or no instincts or survival functions could be exercised at all. The ways in which such a state could be produced are of course unknown, but among them might well be physiological, chemical, or electronic factors.

The patient would be aware of nothing to interest him or to give him feelings of aliveness and actuality. Residual feelings of unworthiness, intense depression, and depersonalization could be anticipated, insofar as there was machinery for activating them.

The nervous system could be expected to participate in a desperate effort to find some way to operate at least some of the instincts. By devious routes, sign stimuli of some kind would be found, if possible. Some part of the body, like the hair, with its delusional associations, might be found; if it worked, the patient might feel that his life had virtually been saved.

Thus, the delusion, with its huge psychological value, would really be the normal result of a normal effort of the organism to preserve its vitality, in the wake of a supposedly nonpsychological disturbance.

A simile might help in making the meaning clearer. One can imagine a man buried by an avalanche, the rocks having fallen so as to leave him transiently safe in a tiny cave a hundred feet down. The victim taps, and rescuers on the surface can just hear the sound. Through this devious route the victim is able to communicate with the outside world.

In the schizophrenic patient the danger of removing this multieffective sign stimulus, assuming that it were possible, is evident.

B. Simple Schizophrenia: It is possible to view these cases as similar to those in Group A, but they do not find the substitute sign stimulus. Hence, they merely sit inertly and gradually deteriorate.

Some Related Points: The resistance to recovery and the reluctance patients often have to relinquish symptoms during psychotherapy may also be interpreted according to these biological concepts.

The "value of illness" receives a further explanation. It is not that patients want "to stay sick." The appetitive phase of the instinct is the "wanting"; an

appetitive search can represent a person's only feeling of vitality or ability to function at all. In a case like that of the patient with the hair delusion, it is virtually the only real life the patient feels, and the operation of the sign stimulus of the hair is almost the only way he can function as a person. Certainly in many nonschizophrenics the search and the patient's usage of the sign stimulus possess a similar value and constitute a sufficient proportion of what seems vital to the patient, to render its loss a great threat.

EVIDENCE FROM NARCOSIS STUDIES

Evidence supporting these hypotheses is drawn from studies of certain characteristics of amobarbital narcosis. Among the operations of the narcotized brain is a ceaseless process which acts upon intellectual units stored in the brain; by this process, which is a systematic one, these intellectual units are split into fractions and recombined into new wholes.

This splitting and recombining applies to both words and ideas. It may be exemplified by the word "obsiden," uttered under narcosis and explained at the time by the patient as coming from "obscure" and "hidden." This is what is usually called a slip of the tongue, or condensation, but that is not the real point; the narcotized brain produces these fracturings and recombinings not just occasionally or "accidentally," but in such great quantity that they must be considered characteristic products of the narcotized brain. Splitting and recombining characterize the whole cerebral activity under conditions of narcosis. Supposedly, these processes go on (although the direct evidence for it is only suggestive) constantly in the normal waking brain too but are either concealed or modified by other brain activity which seems to be in abeyance during narcosis. Under narcosis this type of activity gives every appearance of being predominant, however; either it is actually predominant, or the other processes which normally obscure or modify it are in abeyance.[10]

More than 70 patients with various types of mental and emotional disturbance have been treated by a certain carefully designed procedure making use of amobarbital. The method was originally called "narcoplexis," because it seemed that a "direct hit" could be made upon a psychological constellation when the patient was narcotized.[11] The reading to the narcotized patient of prepared scripts, with specifically planned content, appeared to cause abrupt and often lasting changes in these constellations. The patients' productions in each session while still awake, while being narcotized, and while waking (wake-up period) were recorded, and these, as well as written-out dreams, were annotated; the main annotations were tabulated in charts.

Reevaluation of the substance of these sessions suggests an alternative explanation to that of the "direct hit." All of the therapy was done while the splitting and recombining operations of the brain were predominant, and not concealed or detectably modified to any marked extent by other processes. The question arises whether the usually sudden therapeutic effects were primarily the consequence of splitting off the operations of one group of neural networks from another. Psychologically, these would be called dissociations; here it refers to splitting the previously fused working of two brain structures.

Specifically, were learned sign stimuli sometimes split off from instincts?

If so, then the subsequent events would have to be from the following alternatives:

A. The manifestation of the instinct would drop to a lower level or cease.

B. (*a*) The instinct would never be manifested again or, if it were, only to a minor extent.

(*b*) A new sign stimulus would be attached to the instinct by the "narcoplectic" procedure, in the form of a recombining.

(*c*) The patient himself would gradually learn a new sign stimulus. Either *b* or *c* would, of course, permit the instinct to be expressed actively again.

(*d*) The instinct would permanently lose its dominating influence. New instincts or survival functions would have a chance to become ascendant, either merely by being released from domination or through the learning of new appropriate sign stimuli by a patient now freed to learn them.

REPORT OF CASES

Dependence.—In several cases a sharp drop in infantile dependence occurred abruptly during treatment. These were associated with concomitant changes in regular waking behavior.

In most instances involving the survival function of dependence the change followed scripts which dealt with a parent of the patient in one of two ways:

A. A very loving situation involving patient and parent was described. Oftenest this was in the form of a nursing scene; sometimes it merely depicted as loving and affectionate a parent who was actually not so or did not seem so to the patient. In the cases now alluded to, after several sessions in which such a script was used, the patient rejected the idea of the script, belittling the authority of the parent who was the principal center of his dependence.

The rejecting comments would occur in wake-ups during the time of change; dreams at the same period had content describing or otherwise dealing with the overthrow of the supreme authority of the parent.

Sometimes the drop in dependence was abetted by scripts describing weaning in sessions immediately subsequent to those employing nursing scripts.

B. A direct assault upon the parent, even including killing. Often, the immediate reaction was the concept that the hitherto untouchable authority of the parent no longer was wanted and no longer existed.

Sometimes the drop in dependence was associated with a transient trend of fear, rage, or depression.

In almost every case, the reduction in dependence was followed, usually considerably later, by a marked improvement in the patient's relations with the former authority; the relationship became more realistic, affectionate, companionable, and pleasant.

The cases can be outlined only scantily here, and only the most relevant material can be touched upon.

CASE 1.—The patient, a man of 28, had so great an infantile dependence on his mother as to be virtually unable to function except in relation to her. Even his career was devoted to carrying out major attitudes of hers.

During the two months of "narcoplexis" (eight weeks, with two sessions weekly) this state of dependence dwindled almost to the vanishing point, and in the early part of waking follow-up sessions it seemed to disappear altogether.§ The mother complained that the doctor had taken her boy away from her.

There has been no return of the dependent state in the four years since treatment ended. Instead, the patient passed through a period of resentment of his mother and then entered a peaceable, even affectionate, relationship with her, with what appears almost total emotional independence of her. This has now persisted for more than two years.

Soon after the end of the original dependent state, the patient had a rather severe depression, lasting several months. He welcomed a reorganization at his place of work, which left him without a job; although he had formerly been an "obsessive" worker, now his interest in working at all vanished altogether and he even resented the idea. He turned down several attractive offers.

He developed a new interest a little later, though it has never equalled his old zeal.

The situation falls readily into an interpretation within the framework of this paper. Regardless of interpretations, the actual fact is that dependence was the major discernible survival function on which this patient operated; it was manifestly more important to him than sex, or even rage, which perhaps came next in order. The interpretation now offered is that, as a consequence of treatment, the major sign stimulus (his mother) was split from his most dynamic survival function. The operation of this survival function ceased, leaving him relatively inert, without a reason for exertion or enjoyment, with virtually no way to arouse an intellectual or emotional interest in anything.

In all these latter respects, he resembled, dynamically, the hair-delusion case mentioned above. However, he went on to develop new, normal sign stimuli for other survival functions, in this instance that group related to the self and its importance.

CASE 2.—A woman of 40 had been unable to break the bonds with her parents and siblings and guiltlessly to transfer her affections and loyalty fully to her husband and daughter.

The sudden therapeutic change occurred after several scripts describing nursing scenes, with a marked drop in dependence and in the authority of her family. Concomitantly she blossomed in her roles as wife and mother, her relation with her husband entering an "idyllic" state.

Two weeks after the narcosis series ended, she became depressed rather suddenly, with some conscious feeling of guilt at deserting her mother, after having been so accused. Feelings of unworthiness appeared and grew. Yet the old emotions of infantile dependence did not recur, at least in any detectable form; instead, intense resentment against the members of her old family developed. But at the same time she lost her new capacities as wife and mother. She could move neither forward nor backward but seemed to stand still; she was spoken of as being like a moon stopped in its orbit.

Gradually improvement developed with waking psychotherapy, aided by methamphetamine (Methedrine) and the use of three more amobarbital injections. A new point in technique was also employed, with which the experience is still too small to warrant more than mention. There was a sudden and lasting change immediately after this was done, but the improvement rate had already been accelerated for two days.

Fear.—The relief of chronic fear, in certain cases, can also be interpreted as due to splitting off of sign stimuli from instincts.

There is some overlapping between these cases and cases in other groups. Virtually no case can be so isolatedly defined as to be without linkage to some other groups. The fear cases to be mentioned could perhaps have been grouped with those of overdependence.

§ This patient was treated before the charting system was developed, and it is therefore uncertain whether the changes were sudden, as in the other cases, or merely rapid.

CASE 3.—This case has already been reported in another connection.

A woman of 30 lived in a chronic state of such fear that most stimuli of any kind produced terror. On her chart it took two lines to record all the fear notations.

The patient's fear was basically centered around her father. He had literally frightened her a great deal in her younger days. Her many wishes to become closer to him were accompanied by fears of a return of the old frightening situations and of plain rebuff. That she continuingly and appetitively sought her father, as the sign stimulus for several instincts, seems plain.

A script was read in four successive sessions, depicting an affectionate relationship with a kindly father. The patient's comments regularly showed rejection of this idea. Finally, after the fourth of these sessions, she declared: "I looked up at the Doctor from Amytal position and asked him what to do about my difficult parents. He said, 'Let them go.'" With this dream sharp and marked changes occurred, which proved to be lasting (five-year follow-up). Fear, rage reactions, guilt, and inferiority feelings dropped markedly, and feelings of well-being and independence and general freedom to function rose greatly.

The interpretation is that the father, as a sign stimulus, was split off from the instinct of fear, the rest of the consequences following in the wake of this split.

CASE 4.—A man of 30 presented a situation too complex to outline even briefly, but a severe, unloving father was the manifest focus of many fears.

After a script in which this father was protrayed as violently done away with, many changes suddenly appeared in the patient's behavior trends; the nature and suddenness of the changes were very clear on the chart. Among them were marked drops in anxiety and depression. The changes endured for about one and one-half years, after which there was a brief recurrence.

The interpretation, from the present point of view, is the same as in Case 3.

The available material is replete with examples. Several more relate to dependence and to fear. Many are connected with other survival functions, such as the very complex survival functions relating to the self as such, to identification in particular, and especially to gender identification. These will be discussed fully in a later communication.

SUMMARY AND CONCLUSIONS

Relatively new biological observations and hypotheses are employed in studying certain aspects of human behavior. Through this study, some behavior patterns, both disturbed and otherwise, may be given a biological and uniform type of interpretation.

These hypotheses developed have the following advantages:

(*a*) They may approximate the actual truth.

(*b*) They provide a regular biological rank for a number of disturbances conventionally classified according to psychological rather than biological systems, with roots pictured as lying only in other psychological systems.

(*c*) Conventionally, the deviant or pathological aspects of the disturbance are not seen themselves as representing any regular, normal biological activity; according to this view, they do.

(*d*) The hypotheses make possible a reclassification of various conditions which clinically seem divergent, but which are dynamically closely related when seen from the present viewpoint.

(*e*) They suggest a direct therapeutic approach.

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Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Raymond D. Adams, M.D., President, Presiding
Regular Meeting, Nov. 30, 1953

Formation, Flow, and Reabsorption of Cerebrospinal Fluid in Man. Dr. William H. Sweet and Dr. Herbert B. Locksley.

On the basis of data obtained from multiple simultaneous isotopic tracer studies in man, including labeled water, various electrolytes, and radioiodinated human serum albumin, we have been led to a theory of cerebrospinal fluid formation, flow, and reabsorption which varies from current concepts. We have evidence that cerebrospinal fluid is elaborated throughout the cerebrospinal fluid system, independently of flow from one area to another. It is derived both from the choroid plexus in the ventricles and from structures bordering on the subarachnoid space. Furthermore, we have demonstrated that the reabsorption of water and electrolytes from the cerebrospinal fluid occurs throughout the system independently of flow. These elements of the fluid enter and leave the subarachnoid space by direct molecular capillary exchange and hence may be considered to be in a state of dynamic equilibrium with plasma, similar to that of other fluid components of the body.

The data presented are derived mainly from two patients in whom we found it possible to isolate the lateral ventricles, on the one hand, from the subarachnoid space, on the other. In both patients tumors filling the third ventricle had completely blocked cerebrospinal fluid outflow from the large lateral ventricles over five years ago. At that time a Torkildsen-type ventriculocisternostomy was carried out.

The small plastic tube which we used permitted cerebrospinal fluid to by-pass the block, and the intracranial pressures in both patients had remained essentially normal in the ensuing five years. We were now able to clamp the tube and preclude direct flow between ventricles and the subarachnoid space.

On the basis of studies in which we injected our isotopes either into the blood stream or into the cerebrospinal fluid compartments, we formed the following conclusions: 1. Water and electrolytes enter the cerebrospinal fluid rapidly, both in the ventricles and throughout the subarachnoid space. The formation of the fluid is, thus, not an exclusive prerogative of the choroid plexus. 2. Water and electrolytes pass directly into the blood from both the ventricles and the subarachnoid space. 3. Cerebrospinal fluid does not suddenly come into being fully formed at any point, with all its constituents in proper ratios, but each constituent is exchanging with blood at its own characteristic rate. 4. In contrast to water and electrolytes, protein is absorbed largely from the subarachnoid space, presumably from the arachnoid villi. The site and rate of protein reabsorption is thus an important determinant of the direction and rate of flow of cerebrospinal fluid. 5. The net amount of cerebrospinal fluid elaborated per day in the ventricles, over and above the large equivalent volume exchanged, is small.

This paper was published in full in *Proceedings of the Society of Experimental Biology & Medicine* (**84**:397-402, 1953).

DISCUSSION

Dr. James B. Ayer: I fear I am sadly out of date in the interpretation of spinal fluid production, flow, and absorption with the use of heavy water as the index. Like most others, I have accepted the conclusions of Dandy and Blackfan as to the choroidal origin of the cerebro-

spinal fluid. Although the presence of cerebrospinal fluid in the absence of choroid plexus was thereby difficult to explain, Weed's postulate that some fluid is derived from pericellular and perivascular spaces was an acceptable explanation. There is highly suggestive evidence that the origin of hematogenous meningitis is primarily ventricular, i. e., that ventriculitis precedes meningitis; but this brings up the question of infection, which is not the subject of the present discussion.

DR. WILFRED BLOOMBERG: What consideration has been given to the basic situation that required the use of the Torkildsen tube in altering the hydrodynamic situation? I assume that this occurred in cases of third ventricle tumor blocking the flow of spinal fluid. Would you comment on the pressure relationships that might have occurred in this situation and the effect they might have had?

DR. GILBERT HORRAX: I am speaking from the clinical situation. In the first place, we have known for many years that in instances of hydrocephalus if one removed the choroid plexus one would get a cessation of hydrocephalus. I wonder how the authors would explain that result. Second, in these patients with the tube from a verified third ventricle tumor, is it certain there is no communication between the lateral and the fourth ventricle? Sometimes you do get a partial communication, and patients might live several years. Did they have x-ray treatment and thus let fluid through? Was there an actual block of the system?

DR. EDGAR A. BERING JR.: The estimation of the amount of cerebrospinal fluid produced by drainage is open to serious question. The amount of fluid produced is directly proportional to the pressure of the drainage system. This has been demonstrated in cats by Flexner, and I have found it to be true in patients on constant ventricular drainage.

What happens to the tracers in the cerebrospinal fluid after they reach equilibrium with the blood? Does the specific activity of the tracer in the cerebrospinal fluid fall with that in the blood?

DR. CLEMENS E. BENDA: Most of the younger people have grown up in the concept of Dandy and Weed on the production and circulation of the spinal fluid, which Dr. Selverstone even called the "classical" theory. It may be worth while to remember that the classical theory considered spinal fluid a very important medium of nutritional exchange, comparable to the lymph circulation in other body organs, and that most of the European schools of thought not only consider the spinal fluid as a mechanical water jacket to protect the brain but think that the spinal fluid circulates through the brain parenchyma and is produced and absorbed through many different channels. Although the importance of the choroid plexus is not disputed, the choroid plexuses may well have an important regulatory function without being the sole source of production. In this country Hassin conducted, almost singlehanded, a battle against the "classical" theory of Dandy and Weed, trying to demonstrate that the perivascular spaces had a great importance in the circulation of the spinal fluid and that some of the spinal fluid was produced through the vessel wall from the blood stream and was flowing toward the ventricular and subarachnoid spaces.

Actually, the clinical experiences with hydrocephalus have shown that hydrocephalus cannot be explained merely through anomalies in the choroid plexus or anomalies of absorption through the meninges. Penfield, Hassin, and I showed in independent investigations that in the majority of cases of hydrocephalus a severe degeneration of the choroid plexus is present, and no investigator has ever seen a hypertrophy of choroid plexuses, which ought to be postulated if some of the previous authors were correct.

DR. D. DENNY-BROWN: This reminds me of another session in which our distinguished guest, Sir Geoffrey Jefferson, was present, and we discussed cerebral edema. After a long discussion, he summarized the difficulty by saying: "I still don't understand where all this water in the brain comes from." With the old methods of study, Weed showed that spinal fluid was being produced in large quantities by the choroid plexus, by blocking the pathways of absorption of spinal fluid with carbon particles. It seems to me that in some of Dr. Sweet's data heavy water is behaving much the same as an electrolyte. We start by assuming that heavy water will behave as water. At the cistern the concentration curve shows a delayed component, which

suggests dilution. The question then is what is diluting the heavy water. Is it choroid plexus fluid? That seems to be the essence of this problem. Such a problem could be solved only by isolating either the ventricle or the spinal subarachnoid space.

DR. WILLIAM H. SWEET: Does this isotope behave exactly the same as water?

DR. D. DENNY-BROWN: That is the fundamental question.

DR. PAUL B. JOSSMANN: The differences of potassium concentration in the cisterna and the lumbar spaces may contribute to the explanation of the development and course of familial periodic paralysis.

DR. DONALD D. MATSON: From the clinical point of view, the interesting feature is the suggestion that the absorption of large molecules, that is, of protein, is a specific function of the arachnoid villi. It doesn't make any difference where all this water comes from. How it gets back into the blood stream is more important clinically. Unless cerebrospinal fluid can get to the arachnoid pathways and be absorbed normally there, you are going to have hydrocephalus, no matter at what rate the fluid is formed.

DR. HERBERT B. LOCKSLEY: The conclusions which Dr. Sweet has set forth, despite their contradiction of classical theory, are entirely consistent with the excellent experimental data of workers such as Weed and Dandy, on which the theory is based. Before the present era of isotopic tracers, the technical problems of studying cerebrospinal fluid under even approximately physiological conditions were almost insurmountable, and ingenious nonphysiologic tracers, such as ferricyanide and carbon black, were used to follow the path of flow and reabsorption. It would seem that the classicists were tempted by their data into unsafe extrapolations. When it was demonstrated that cerebrospinal fluid was formed by the choroid plexus, it was concluded that all the cerebrospinal fluid was so formed; and when ferricyanide was consistently observed to find its way to the arachnoid villi, and that "plugging the pores" of the villi with carbon black granules produced hydrocephalus, it was concluded that all cerebrospinal fluid was reabsorbed by this pathway. If our hypothesis regarding the arachnoid villi is correct, they play a specific role in reabsorbing certain large molecules and negatively charged particles, such as protein and ferricyanide. However, to ascribe to them the entire role of reabsorption is as unreasonable as to say that all the interstitial fluid of the systemic capillary bed must return via the lymphatics. The other striking thing to us was the dynamic nature of the relationship between cerebrospinal fluid and plasma. With this concept the choroid plexus then ceased to be a cerebrospinal fluid faucet and became a specialized capillary bed, mediating fluid and electrolyte exchange approximately in accord with the rules of the general circulation. In the course of this exchange there is a certain amount of protein leakage across a very steep concentration gradient. Thus, adequate conditions exist here also to apply Starling's theory of a dynamic balance between hydrostatic and osmotic forces. In this situation, if protein is absorbed at a distance (? arachnoid villi?), local accumulations of protein can produce local changes in pressure and impetus for flow and, in the extreme condition of blockage, hydrocephalus. There may well be other factors contributing to flow, such as a small "filtration pressure" across the barrier membrane (e. g., secretion) and tidal oscillations or pulsations associated with respiration and the cardiac cycle.

DR. WILLIAM H. SWEET: One may ask how reasonable it is to draw conclusions with respect to normal mechanisms from these patients with tumor. We hope that neoplasms in a relatively static state for five years have modified the normal processes to a minimal degree. Dr. Horrax asked how we could be certain that there was no communication between the lateral and fourth ventricles. We determined this by injecting indigo carmine into the lateral ventricles in each patient. The dye stained the lumbar samples faintly only after several hours. This may possibly have been due to a slight leak along the Torkildsen tube, between the ventricle and the subarachnoid space. In any event, we have this evidence that the block was nearly complete.

Concerning the choroid plexuses, we do agree that they have a major function in exchanging electrolytes and water; this has long since been demonstrated by the fact that their removal arrests or improves hydrocephalus in many patients. Dr. Denny-Brown's question as to whether or not our tracer substances behave like the normal substances lies at the core of all tracer work. A discussion of it would take us a little far afield, but I may say that we are planning to carry

out comparative studies using H_2^2O and D_2O, since the heavy forms of water perhaps differ from each other and from their physiologic counterpart, H_2O, more than any of the other tracers used differs from its normal stable isotope. If the two forms of heavy water behave similarly, we should have more evidence that they, the labeled isotopes, are a valid mirror of the behavior of the substances present normally.

We should like to emphasize that the large volume of the ventricles in our patients resulted in a slower rate of change of concentration of tracer there than in the subarachnoid space for equal rates of passage of ions into each cubic centimeter of cerebrospinal fluid. Thus, in Patient S. P., although after intra-arterial injection Cl^{38} was rising in concentration in the subarachnoid space as rapidly as in the lateral ventricles, the latter had about eight times the volume of the former. Hence Cl^{38} was entering into the lateral ventricles eight times as fast as into the subarachnoid space.

Dr. Jossmann commented on differences in potassium concentration. I should make it clear that the differences shown in our data refer only to labeled potassium, K^{42}, and are not intended to indicate the total content of concentration of physiologically effective potassium ions.

I should like to thank all the discussers for their comments and searching questions.

Trigeminal Neurinomas. PROF. SIR GEOFFREY JEFFERSON, F.R.S., M.S., F.R.C.S., F.R.C.P.

No abstract of this paper is available.

PHILADELPHIA NEUROLOGICAL SOCIETY

Alexander Silverstein, M.D., *Presiding*

Regular Meeting, Dec. 4, 1953

Chiasmal Lesions Produced by Intracranial Aneurysms. PROF. GEOFFREY JEFFERSON, London.

Aneurysms affected the chiasm or visual gateways in about 1 in 10 cases of the Manchester series of 265 patients with aneurysm. Sometimes a clue revealing the site of the aneurysm could be found in cases of depressed visual acuity in the ipsilateral eye in the acute stage of bleeding of anterior cerebral aneurysms. In a previous communication I published an account of 12 personal cases of interference with the visual gateways and had collected 66 examples from the literature. I am presenting 14 additional cases. Bitemporal hemianopsia of the sort seen in patients with pituitary adenoma was found sometimes, but the commoner effect was either some variety of inferior altitudinal hemianopsia or homonymous hemianopsia. In either case an important feature was a strong tendency for visual acuity to be greatly diminished on the side furnishing the aneurysm while acuity remained good in the contralateral eye. The disparity was greater than in the general run of pituitary adenomas. This was illustrated by a scheme showing the acuities and field defects in the series. (The speaker went on to discuss in some detail the patterns presented by his cases.) The fields were sometimes bizarre, and diagnosis could be particularly difficult in patients who had no head pains and gave no history of subarachnoid hemorrhage. Bilateral angiography should be carried out on most patients with unexplained optic atrophy, except in the aged hypertensive patient.

Sometimes a considerable improvement in vision could be brought about by carotid ligature. Where the aneurysm fills equally well from either side, or when ligature fails to improve vision, I favor a direct attack. In the whole series ligature had been used 7 times and direct attack 10 times; in 6 cases nothing was done, for various reasons. Of the new material, one with ligature died suddenly 5 years afterward, presumably of a fresh hemorrhage; one died 5 years later (the aneurysm had thrombosed but was very large, filling the interpeduncular space); the remainder were alive 15, 10, 7, 5, 3, and 2 years later, respectively. Of the patients treated by direct attack, one died at once of hemorrhage from a second aneurysm in the posterior fossa; of the others, all whose aneurysms were removed are alive; the longest survivor has lived 10 years.

DISCUSSION

DR. J. RUDOLPH JAEGER: I must compliment the speaker on the presentation of such an informative and well-arranged paper. It is apparent that some surgeons still believe in carotid ligation. In the last two cases of carotid ligation which I performed for such aneurysms as these, a propagating clot in the internal carotid artery entered the brain and killed the patient. This makes carotid ligation exceedingly hazardous. It will take years to figure out the right answer to the problem. We will all admit that Sir Geoffrey is a master in this subject and its presentation.

DR. HELENA RIGGS: The aneurysms that we have dealt with have been of the miliary type and were associated with leakage. Of 140 cases only one patient had blindness. This was apparently due to adhesions which resulted from the escape of blood around the optic nerves.

DR. BERNARD J. ALPERS: Sir Geoffrey said nothing about the diagnosis of aneurysms. I have come to feel that aneurysms can be imitated by many other lesions. At present we are analyzing 11 cases which presented typical clinical pictures of intraclinoid aneurysms. However, subsequent investigation failed actually to demonstrate aneurysms, and these cases were in the category of ophthalmoplegic migraine. With regard to the effects of ischemia on the optic chiasm, we have studied the oculomotor nerve in aneurysms compressing this structure and have not found any demyelination in the nerve.

PROF. GEOFFREY JEFFERSON, London: Because of the limitations of time, I did not get to a discussion of the differential diagnosis of aneurysm and tumor. In my experience the propagation of a thrombus is exceedingly rare. In the last two years we have performed carotid ligation in 68 patients. Fifty patients tolerated this procedure without hemiplegia. Of the 18 patients who did develop hemiplegia, 1 died.

Charles Rupp, M.D., *Presiding*
Regular Meeting, Feb. 5, 1954

Probable Origin and Purpose of the Superficial Reflex, Known as the Sign of Babinski. DR. TEMPLE FAY.

Slow motion picture comparison of lower vertebrates, especially amphibian types, indicates that extension of the big toe and the fanning movement of the webbed foot, characteristic of the "sign of Babinski," appears as part of a free swimming propulsion cycle. Contact of the outer skin surface of the foot with a resistant medium or firm surface initiates a reflex of extension and spread of the digits so as to make possible more effective motor expression.

Every normal human infant is born with this "phenomenon of the big toe," known as the "sign of Babinski," and retains this response until higher levels of vertebrate evolution assume control. The highly integrated reflex portion of the lumbosacral portion of the cord may function independently at the amphibian level when higher centers have been removed by pathological conditions, thus permitting reappearance of this primitive portion of the reflex cycle. The early vertebrate manifestations of big-toe extension can be traced to a period 300 million years ago, and the sign of Babinski can be considered as normal for this level. The newborn infant recapitulates the evolutionary picture before later additions of motor controls have become established at higher levels.

DISCUSSION

DR. E. A. SPIEGEL: I have always been interested in Dr. Fay's phylogenetic interpretation. I recently translated a letter from a German professor in which he stated he felt that Dr. Fay's concepts were better than Foerster's.

DR. HENRY WYCIS: This study is a painstaking one. I remember well that Dr. Fay, my teacher, showed me how to elicit a Babinski sign properly. One case that comes to mind was interesting in that the Babinski sign was only elicited when the stimulation was applied along the first sacral arc. When I got over to the fifth lumbar arc, it disappeared.

DR. TEMPLE FAY: We ignore the earlier beginnings of the nervous system when we were belly side down. Dr. John Fulton frequently elicits the Babinski sign in the sitting position.

One can sometimes get this sign by stimulating as high as the thigh. In the new resistance therapy they are beginning to appreciate the origin of this sign. The Babinski sign is a hold-over from the early states. These reflexes belong to the protective group of the nervous system of 300 million years ago.

Tuberculomas of the Cerebellum. Dr. George M. Austin and Dr. Francis C. Grant.

In North America cures of tuberculomas of the central nervous system have been decidedly rare among cures of mass lesions of the brain. Previous American authors, including Cushing, Bailey, Van Wagenen, Adson, and Dandy, have recommended conservative handling of these lesions. Thus, if any surgery was to be done, they advocated merely subtemporal decompression. This was primarily due not to their difficult extirpation but to the likelihood of a subsequent tuberculous meningitis. The high mortality of the latter was notably decreased with the use of streptomycin, starting in 1945. Recently this has been combined with paraaminosalicylic acid (PAS). Finally, with the development of isoniazid the previous mortality of tuberculous meningitis was still further lowered.

We have reported two cases of tuberculoma of the cerebellum in young Negro males without signs of tuberculosis elsewhere. These lesions were totally removed at operation, and the patients were subsequently given intensive medical therapy. Both received intrathecal streptomycin, in addition to intensive intramuscular therapy. They also were given large doses of PAS. One of the patients received, in addition, isoniazid. Both patients have been followed for more than one year without signs of recurrence or meningitis, and both are gainfully employed.

DISCUSSION

Dr. Charles Rupp: I think this paper shows how the value of treatment has been enhanced by new drugs. The patients we reported were not operated upon because tuberculous meningitis would have developed and they would have died. Those patients who were operated upon were thought to have tumors. These tuberculomas are not uncommon, even today. They occur in older Negroes, and not so much in the younger age group. Not all the earlier operative cases were fatal. We had a patient at Graduate Hospital who had been operated upon 20 years before by Dandy and who now showed no evidence of tuberculosis.

Dr. Robert A. Groff: I should like to ask a question. Is it necessary to remove these lesions now that antibiotics are successful?

Dr. Henry Wycis: I am not in agreement that removal would precipitate tuberculous meningitis, even before streptomycin. Dr. Fay removed a tuberculoma from the parietal lobe and had a good result, and I remember a second case, of a tuberculoma in the posterior fossa, in which there was also a good recovery.

Dr. Temple Fay: In how many patients has tuberculous meningitis actually developed in association with the surgical removal of the tuberculoma? I think Dr. Cushing alarmed the neurosurgeons. Although we cannot always make a diagnosis before operation, a spinal fluid chloride level below 624 mg. per 100 cc. makes me feel it is tuberculosis. If we know the lesion is a tuberculoma, we should attack it surgically. I do not think the credit should all be given to the medication. The outcome depends largely on the stage of the tuberculoma with which we are dealing. If it is an active lesion, the results may not be good.

Dr. Matthew Moore: In South America they do not operate on tuberculomas. The tuberculomas calcify early there. They were using streptomycin and PAS. Frequently multiple lesions were found.

Dr. George M. Austin: Beware of the man with two cases. I have the impression that tuberculous meningitis is the commonest cause of postoperative death. As to making the diagnosis preoperatively, one should suspect it in the younger Negroes but should not depend upon finding tuberculosis elsewhere. I agree with Dr. Fay that much may depend on the size of the lesion, the location, and the state it is in. I had an opportunity of discussing the mechanism of these lesions with Sir Hugh Cairns, and he felt that circulating bacteria sensitized the blood-brain barrier and later organisms break through and form a tuberculoma.

Application of Stereoencephalotomy to the Treatment of Cystic Brain Tumors. Dr. H. T. Wycis, Dr. R. Robbins (by invitation), Dr. M. Spiegel-Adolf, and Dr. E. A. Spiegel.

Among the various applications of stereoencephalotomy that we outlined in our first paper, describing a stereotactic apparatus devised for use in patients, was the treatment of subcortical tumors. While the uniform infiltration of a large tumor with radioactive substances still meets with certain difficulties, a rather favorable condition for the injection of radioactive substances exists in the case of cystic tumors, since the agent injected in the cavity can easily act upon tumor cells lining the wall of the cyst. We have attempted to apply this method in the following case: A 12-year-old boy with an inoperable cystic craniopharyngioma is presented. A roentgenogram disclosed a suprasellar calcification. Ophthalmoscopic examination showed early papilledema and a bitemporal field cut. By means of the stereotactic technique the suprasellar cyst was punctured, removing 5 cc. of yellow fluid, which was replaced with 3 cc. of ethyl iodophenylundecylate (Pantopaque) for roentgenographic visualization. The postoperative x-rays showed the ethyl iodophenylundecylate to be collected in a cystic pear-shaped cavity. Headaches and papilledema persisted (3 D., O.D.; 2 D., O.S.). When radioactive colloidal chromic phosphate became available, the cyst was again punctured by the stereotactic technique. Eleven cubic centimeters of milky-white fluid was aspirated and replaced with 9 cc. of P^{32} (colloidal chromic phosphate) containing 1.2 mc. (dose 20,000 rem). One week later the papilledema was reduced to 1 D., with a slight decrease in the visual field defect in the left eye. When reexamined six months later, the boy was attending school and was symptom-free. Papilledema was absent, and the visual field had considerably improved.

Since the mechanism of cyst formation is rather obscure, the enzymatic activities of fluids from various cystic tumors (acoustic neurinoma, craniopharyngioma, astrocytoma, and glioblastoma multiforme) upon both types of nucleic acids, three pyrimidines and two purines, were tested by spectrophotometric methods. Controls were made with normal serum and cerebrospinal and ventricular fluids from various conditions. In a number of cases the action of the cyst fluids upon the tigroid bodies of anterior horn cells was tested in sections of cats' spinal cord. The results vary according to the type of tumor. Practically no enzymatic action against either nucleic acid can be detected in the neurinoma cyst fluid by either method used. Cyst fluids from the other above-mentioned brain tumors show marked nucleic-acid-splitting activity, which reaches its highest values in the group of glioblastoma multiforme. The difference in the enzymatic activities of various tumors runs parallel to the nucleic acid content of the respective cyst fluids, reported by Cummings.

DISCUSSION

Dr. Robert A. Groff: The authors are to be congratulated on their excellent results. This is a step forward, but we should wait awhile, a year or two, say, to see how effective x-ray treatment may be. I cannot agree that this tumor was inoperable. I have removed two-thirds of such a tumor. I should like to see a piece of that tumor wall to see what effect the radioactive material had on it. The paper is misnamed; it should be entitled "Treatment of Craniopharyngiomas."

Dr. Melvin W. Thorner: I had an opportunity to see Dr. Sweet's work with P^{32}. Was the dose that was given in this case comparable to the dose of P^{32} which is given intravenously?

Dr. Matthew Moore: This method is an ingenious one. What were the criteria on which the tumor was judged inoperable? I saw one case in which the tumor was not completely removed, and that man is now working. I saw another case in which recovery was spontaneous. I should like to ask about the perineuronal change. Was there a similar change in perivascular space?

Dr. Temple Fay: I saw one of these tumors at the Naval Hospital. I do not feel that they are inoperable. I believe you should collapse the cyst wall.

Dr. E. A. Spiegel: What is the mortality of the operation?

Dr. Temple Fay: I have never completely removed one, but I would say about 18 to 20%.

DR. ROBERT A. GROFF: I think Dr. Fay's figures are about right; but the important thing in this procedure is that if you have something that will shrink down the tumor and allow the surgeons to go in after it and get it, the procedure is worth while.

DR. E. A. SPIEGEL: We thought a puncture has less risk than operation. We do not believe that a single injection of radioactive substance will be permanent, but these punctures can be repeated. The changes that were seen came from the action directly on the cat's spinal cord. It was not an intravital preparation, but it was in vitro.

DR. HENRY WYCIS: The mortality rate is about 20%, as reported by Love. It is a risk to do surgery in the face of the increased intracranial pressure. If I had tried to operate, we would have had a dead patient. I did not mean to imply that this was a cure.

Charles Rupp, M.D., *Presiding*
Regular Meeting, March 5, 1954

Succinylcholine Chloride Modification of Electroshock Therapy. DR. DAVID J. IMPASTATO (by invitation) and DR. SEYMOUR BERG (by invitation).

Although electroshock therapy has proved to be a very effective treatment, especially for depressions, undesirable complications, particularly fractures, occur in spite of refinements in technique. Search for an effective preventive has been focused on muscle relaxants. The ideal muscle relaxant should be capable of producing adequate relaxation for a brief period, have no cumulative effects, so that the dose can be repeated if necessary, cause no marked change in the respiratory or circulatory systems, and have no other undesirable side-effects.

The muscle relaxants that have been used up to now, namely, curare derivatives, decamethonium bromide (Syncurine), and gallamine (Flaxedil), have been unsatisfactory because they have not met the criteria stated above. The action of decamethonium bromide and curare lasts too long. Curare causes bronchospasm and serious fall of blood pressure. Gallamine does not produce adequate relaxation.

Succinylcholine chloride does not possess any of these undesirable side-effects. Its action lasts only two to three minutes; it is easily administered; it does not require an antidote, and it produces excellent and controllable relaxation. We suggest that when the patient is first treated, a test dose of 5 mg. of succinylcholine chloride be given and that subsequent dosage be gauged according to the response of this test dose. Succinylcholine chloride is an excellent muscle relaxant for electroshock therapy, and we recommend it highly.

DISCUSSION

DR. HARVEY BARTLE: This paper was most interesting. Anything that we can get that is better than decamethonium bromide is welcome. We have used such a machine as that described by Dr. Berg.

DR. ARNOLD LEVINE: We, too, have used succinylcholine (Anectine) chloride. At first we tried it with a patient with a fracture. She was given succinylcholine chloride, and intubation instituted. Since September, 1953, we have used the drug routinely. We still use a mouthpiece and an airway. At first we used the airway alone, and, when a patient broke his front teeth, we added the mouthpiece. We now give succinylcholine with amobarbital (Amytal) sodium. If the face is blue, the brain is blue; so we give oxygen routinely. We use a bag and squeeze it for positive and intermittent pressure. I think this drug has a real place in electroshock therapy.

DR. GABRIEL SCHWARZ: We have used the method with poor-risk patients. I had one patient with a fusion for ruptured disk who developed a psychosis. Another was a patient with cardiac decompensation. Both are doing fine. I should like to ask whether Dr. Impastato has any explanation for the cases in which a dysrhythmia of the heart is produced?

DR. DAVID J. IMPASTATO: The original technique was shown us by Dr. Holt, of Albany. He used the same technique as that described by Dr. Levine. He devised a rubber mouthpiece with a hole in the center for the airway. At Bellevue Hospital we like to simplify techniques. We used this twice in 150 cases and found that we did not need it. Anything placed in the

mouth produces salivation, and that makes trouble. In answer to Dr. Schwarz's question: These arrhythmias occur in 30% of the patients. They come on either immediately after, or a few minutes after, the treatment and last only a few minutes. They are all benign.

DR. SEYMOUR BERG: We have treated at least three patients who had had electroshock therapy and fractures. Another patient had jumped out of a window and was all broken up, but with succinylcholine chloride we had no difficulty. At present we are treating a patient with advanced Pott's disease. Patients actually have said that the pain of their fractures became less as they went along, indicating healing. If you use 20 mg., you get no complications.

Ocular Manifestations of the Arnold-Chiari Malformation. DR. LAWRENCE J. BARROWS and DR. D. G. COGAN (by invitation).

Nine cases of platybasia and the Arnold-Chiari malformation were studied with particular reference to the ocular manifestations of these diseases. The ocular abnormalities may be the presenting symptoms and the only symptoms of these two congenital abnormalities. Clinically they resemble each other and often coexist. Vertical nystagmus occurred in every case, with skew deviation found in three instances. The vertical nystagmus varied with head posture, but this sign is not pathognomonic, since it also occurs with cerebellar tumors. In three of the nine cases a diagnosis of multiple sclerosis was made several years before the bony abnormalities of the skull were detected.

A true lateral projection of the skull, to include the base of the brain and the first three cervical vertebrae, provides accurate measurement of Chamberlain's and Bull's lines. Normally these two lines are parallel, but they transect one another in platybasia. Routine skull films will not show evidence of platybasia. Of four patients operated on, one died after operation, one died five months later, and two were unimproved.

DISCUSSION

DR. HELENA RIGGS: We have had no cases of platybasia in adults. I was interested in acquired platybasias. In Paget's disease (osteitis deformans) one gets a decrease in the foramen magnum. There is some herniation and a great deal of compression. Weigert sections show no particular demyelination. I am interested in why we get clinical manifestations in congenital malformations but none in acquired forms.

DR. JOSEPH YASKIN: What is the cause of vertical nystagmus in these anomalies? We know that horizontal nystagmus can occur in any part of the posterior fossa or in irritation of any of the medial nuclei, but vertical nystagmus means involvement of the posterolateral bundle. We see it in multiple sclerosis and midline cerebellar tumors of children. Is it by indirect pressure on the posterior longitudinal fasciculus, or is it a combination of congenital anomalies?

DR. ALEXANDER SILVERSTEIN: I studied some of these cases. The first was a typical case of multiple sclerosis with Charcot's triad. Autopsy showed marked thickening of the meninges, with occlusion of the blood vessels. In another case what appeared to be syringobulbia turned out to be platybasia.

DR. LAWRENCE J. BARROWS: I cannot add much to the pathology of vertical nystagmus. None of our patients were examined post mortem. There are a number of cases of Paget's disease in rickets which are clinically indistinguishable from platybasias. There are also cases in the literature of a basal meningitis that clinically resembles this.

Observations on the Anatomy of the Cerebral Blood Vessels Which May Influence Cerebral Circulation, with Clinical Interpretations. DR. LOIS A. GILLILAN.

The textbook picture of the circle of Willis and its feeding arteries has many variations. The origins of the three cerebral vessels and their principal source of blood are the variable factors, but the peripheral branches are remarkably constant in location and pattern. The posterior cerebral artery may receive its blood supply wholly or partially from the internal carotid artery. Clinically, its origin from the internal carotid artery should be important in (1) interpreting angiograms where filling of the posterior cerebral artery is seen after carotid injection, and (2) possible sequelae of occlusions of the internal carotid artery.

From specimens of human brains prepared by two new methods, information has been gathered which confirms and emphasizes the variations previously observed and extends our knowledge of the vessels penetrating brain tissue. Major anastomoses of the cerebral vessels have not been observed after six months of fetal development. For practical purposes, the arteries of the brain are "end arteries." Arteries well under 0.5 mm. in diameter either form a fine network stemming from the surface arteries or penetrate brain tissue as small, straight vessels. Deep structures, such as the basal ganglia and internal capsule, are supplied by special arteries of small caliber, branching directly from all three cerebral arteries.

DISCUSSION

DR. HELENA RIGGS: The illustrations are magnificent. They show what a clinician should learn about the cerebral circulation. The areas of cerebral thrombosis and hemorrhage are supplied by blood vessels that are precapillaries. The one place to find thrombosis is in the large surface blood vessels. We had two cases with anomalous connections between the anterior cerebral arteries and the arteries in the falx.

DR. JOSEPH YASKIN: This presentation is a real treat. It is certainly instructive to see the anastomosis of the ophthalmic and middle meningeal, as well as of the external maxillary, arteries. The illustrations of the intimate blood supply of the brain are also excellent. Strokes come on suddenly, and there does not seem to be a correlation between the clinical findings and the pathology. Some day we may find the answer.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

HYPOTHALAMIC INVOLVEMENT IN THE PITUITARY-ADRENOCORTICAL RESPONSE TO STRESS STIMULI. R. W. PORTER, Am. J. Physiol. **172**:515 (March) 1953.

This study was undertaken to evaluate the stress-induced changes in the electrical activity of the posterior hypothalamus which were correlated with a fall in circulating eosinophiles. Cats with chronic hypothalamic lesions were subjected to stressing agents to determine whether the normal adrenocortical response could occur. Efforts were made to determine whether direct hypothalamic stimulation could induce pituitary-adrenal response similar to that seen with stress stimuli. Anterior hypothalamic lesions were without effect. The eosinopenic response to epinephrine, formalin, and histamine was prevented by posterior hypothalamic lesions. It was found that eosinopenia resulted from excitation of the tuberal and mammillary areas, but the surrounding regions failed to give this response. The observations concur with the author's previous findings that electrical activity of the posterior hypothalamus occurs with the administration of stressing agents. It is apparent that the central nervous system participates in the pituitary-adrenal response.

BERRY, Washington, D. C.

PULMONARY EDEMA AND HEMORRHAGE FROM PREOPTIC LESIONS IN RATS. J. E. GAMBLE and H. D. PATTON, Am. J. Physiol. **172**:623 (March) 1953.

Discrete electrolytic lesions of the rostral hypothalamus produced in rats fatal hemorrhagic edema of the lungs. Hyperthermia, a common concomitant of rostral hypothalamic lesions, was eliminated as an essential contributing factor to the edema. Neither lesions bordering the preoptic region nor unilateral preoptic lesions produced pulmonary edema. Effective lesions were bilaterally situated at the lateral tips of the rostral third of the optic chiasm. In a few animals, more caudally placed lesions in the midline destroying the periventricular system produced edema, such lesions, according to the authors, producing their effects possibly from the interruption of the descending pathways from the critical preoptic region.

BERRY, Washington, D. C.

PHYSIOLOGICAL ADAPTATION TO COLD OF PERIPHERAL NERVE IN THE LEG OF THE HERRING GULL. P. O. CHATFIELD, C. P. LYMAN, and L. IRVING, Am. J. Physiol. **172**:639 (March) 1953.

The authors investigated conduction as a function of temperature in excised superficial peroneal nerves of herring gulls. In these birds the environmental temperature was found to have a profound effect on the temperature of the unfeathered metatarsal portion of the leg, without significantly affecting the deep abdominal or tibial temperature. The nerves showed a gradient to resistance to cold, the more distal segments conducting at much lower temperatures than the more proximal. The prominence of this gradient was directly related to the coldness of the environment in which the birds had been experimentally maintained. It is concluded that the functional resistance to cold in the nerve to the metatarsus in these birds is the result of some process of adaptation occurring during exposure to low temperatures. Histochemical study failed to reveal any difference in chemical morphology between tibial and metatarsal portion of nerve. Species differences were found; no gradient in resistance to cold was apparent in comparable nerve in the domestic hen.

BERRY, Washington, D. C.

KINETICS OF SOUND-INDUCED CONVULSIONS IN SOME INBRED MOUSE STRAINS. J. L. FULLER and M. E. SMITH, Am. J. Physiol. **172**:661 (March) 1953.

Four mouse stocks were tested for susceptibility to audiogenic seizures. Animals were tested with and without previous auditory "priming stimulation." Five- and 10-second priming produced distinct enhancement of susceptibility, as shown by reduced test latencies. Twenty-second priming produced a gradual decrease in susceptibility, reaching a maximum after 40 seconds of silence. Susceptibility returned to nearly normal levels after 80 to 100 seconds. The strain differences of inbred mouse stocks are described in terms of cumulative frequency curves of their seizure latencies. The results described indicate that the time relationships of sound-induced convulsions in inbred mouse strains are highly predictable under a given set of circumstances.

On the basis of their observed results the authors present a formal theory: It is assumed that a convulsion will occur whenever more than a critical number of motor units are activated simultaneously. Impulses arising in the acoustic nerve continuously produce such activation if their frequency is above a certain minimum. The anatomic nature of these acousticomotor circuits is unknown, but their existence is demonstrated by the reactions of the subjects. As additional circuits are recruited, convulsions would inevitably occur were it not for a process of blocking which on the average occurs 10 to 15 seconds after activation. The locus of this blocking is not identified. This explains the difference between 5-second priming and 15- or 20-second priming. Gradually the reservoir of unexcited circuits is depleted and further stimulation is noneffectual. Once activation of the circuits occurs, they must remain hyperexcitable for periods up to one minute, for resumption of stimulation leads to an accelerated build-up of the typical convulsion. The occurrence or nonrecurrence of a convulsion is regarded as due to the balance between circuit excitation and circuit blocking, both processes being related statistically to differences in genotype.

BERRY, Washington, D. C.

THIRST TESTS IN DOGS AND MODIFICATIONS OF THIRST WITH EXPERIMENTAL LESIONS OF THE NEUROHYPOPHYSIS. E. F. ADOLPH and A. B. KELLER, Am. J. Physiol. **173**:233 (May) 1953.

Adolph and Keller studied the urge to drink and its modifications in normal dogs and compared these normal animals with dogs in which lesions of the neurohypophysis had been made, producing varying degrees of diabetes insipidus. It was demonstrated that certain lesions produced abnormalities of drinking independent of the processes of urinary excretion, thus identifying a specific neural and hormonal basis for thirst. Neurohypophyseal lesions were highly specific in their influence on thirst, exaggerating the intake after water deficit but not after salt excess. The stimuli to drinking used were hydropenia and hypercholia; vasopressin (Pitressin) and the neurohypophyseal lesions enhanced the former, not the latter. Vasopressin alone is not a stimulant to drinking, and no component of vasopressin is, by itself, a regulator of drinking. The overdrinking dog is still subject to inhibition from gastric filling, and the authors conclude that the stalk of the hypophysis is not the only pathway of gastric influence.

BERRY, Washington, D. C.

ACTION OF SEROTONIN (5-HYDROXYTRYPTAMINE) ON VAGAL AFFERENT IMPULSES IN THE CAT. J. A. SCHNEIDER and F. F. YONKMAN, Am. J. Physiol. **174**:127 (July) 1953.

The vasoactive substance serotonin (5-hydroxytryptamine) uniformly produces bradycardia, fall in blood pressure, and respiratory arrest occurring at the same instant, followed by tachypnea. This effect is influenced characteristically by different kinds of blocking agents. Atropine antagonizes the blood pressure fall and, in some cases, the bradycardia. Ganglionic-blocking agents reverse the normal depressor action of serotonin, but the heart remains unchanged. Neither agent antagonizes the respiratory arrest; in fact, ganglionic blockade prolongs the respiratory arrest. Intravenous local anesthetics in high doses antagonize all three effects of serotonin. It is assumed that the effect of serotonin in cats is directly the result of stimulation of the autonomic sensory nerve endings. The action of serotonin on the heart is not inhibitory. The authors obtained direct evidence of stimulation of vagal afferent fibers from stimulation of pulmonary stretch receptors.

BERRY, Washington, D. C.

BRAIN METABOLISM DURING ACCLIMATIZATION TO HIGH ALTITUDE. H. G. ALBAUM and H. I. CHINN, Am. J. Physiol. **174**:141 (July) 1953.

Rats were acclimatized to lowered barometric pressure equivalent to 11,000, 18,000, and 22,000 ft. There was no significant alteration in the levels of the following brain constituents: inorganic phosphorus, phosphocreatine, organic phosphorus, glycogen, lactic acid, adenylic acid, adenosinediphosphate (ADP), adenosinetriphosphate (ATP), hexose diphosphate, glucose-1-phosphate, and diphosphopyridinenucleotide. There was no change in activity of brain cytochrome oxidase, and the rate of P^{32} incorporation into brain ATP was unaltered. Nitrogen breathing for three minutes decreased brain ATP, ADP, phosphocreatine, organic phosphorus, and gylcogen, but inorganic phosphorus, lactic acid, and adenylic acid increased correspondingly.

BERRY, Washington, D. C.

INFLUENCE OF SENSORY NEURONS ISOLATED FROM CENTRAL NERVOUS SYSTEM ON MAINTENANCE OF TASTE BUDS AND REGENERATION OF BARBELS IN THE CATFISH. R. P. KAMRIN and M. SINGER, Am. J. Physiol. **174**:146 (July) 1953.

Degeneration of taste buds in the catfish, as noted after denervation, does not occur after interruption of the central root of the nerve of supply when this takes place without destruction of the neurons or the peripheral connection. Regeneration will not occur after section of nerve supply peripheral to the ganglion, but the amputated barbels (which contain numerous taste buds) are capable of regeneration if the interruption is of the central root. The authors conclude that the neural influence which is necessary for the maintenance of integrity of the taste buds and barbels does not emanate from the central nervous system, nor does it require central connections, but must arise within the neuron of supply.

BERRY, Washington, D. C.

SPINAL PATHWAYS FOR PROJECTION OF CUTANEOUS AND MUSCULAR AFFERENTS TO THE SENSORY AND MOTOR CORTEX OF THE MONKEY. E. D. GARDNER and F. MORIN, Am. J. Physiol. **174**:149 (July) 1953.

Gardner and Morin have previously demonstrated in the cat that complete section of the dorsal funiculi fails to abolish the cortical projection of sensory impulses from muscles, that each ventrolateral funiculus conducts impulses from deep and superficial nerves of both hindlimbs to somatic Areas I and II of both cerebral hemispheres, and that similar results are obtained for afferent projections to the midbrain and to the anterior lobe of the cerebellum.

The findings in the Macacus mulattus substantially confirmed the results obtained in the cat. In two experiments potentials recorded from the precentral gyrus persisted after removal of the postcentral gyrus bilaterally. The authors conclude from the results of this study that "impulses of different modalities can ascend in the ventrolateral region of the cord and that in addition to spinothalamic fibers there are others, presumably spinoreticular, which relay in the lower part of the medulla oblongata."

BERRY, Washington, D. C.

SPINAL PATHWAYS FOR CEREBELLAR PROJECTION IN THE MONKEY. F. MORIN and E. D. GARDNER, Am. J. Physiol. **174**:155 (July) 1953.

The spinal pathways to the anterior lobe of the cerebellum of the Macacus mulattus were studied by oscillographic methods. The results indicate that the areas of projection of both deep and superficial afferent impulses are coextensive in the anterior lobe. Both types of impulses can reach the same cerebellar area through either ventral quadrant of the cord. The study of chronic lesions of the spinocerebellar pathways reveals no gross functional deficit and supports the idea of very considerable compensation. Because both deep and superficial nerves share a common area of projection in the anterior lobe of the monkey and the cat, in agreement with the findings for the projection in the sensory and motor cortex of the monkey, the authors conclude with Mountcastle that no separate specific central areas exist for superficial and deep sensory projections.

BERRY, Washington, D. C.

EFFECTS OF CLOSE ARTERIAL INJECTIONS OF ACETYLCHOLINE ON THE ACTIVITY OF THE CERVICAL SPINAL CORD OF THE CAT. W. FELDBERG, J. A. B. GRAY, and W. L. M. PERRY, J. Physiol. **119**:428 (March) 1953.

The authors studied the effects of injections of acetylcholine into the cervical spinal cord via the basilar artery ("close arterial injection") on the activity of the cord as recorded electrically from the ventral rootlets of the first cervical nerves. In doses of 0.2 ml. of 10^{-4} solution, acetylcholine caused changes indicating potentiation of excitatory processes. For example, it caused an outburst of impulses lasting for 2 to 40 seconds, an increase in the base line fluctuations, an increase in the area and a decrease in the latency of the electrically excited ipsilateral reflex, an increase in the amplitude of the ventral root potential, and a decrease in the interval between the stimulus and the peak of the root potential. These effects were prolonged by physostigmine and neostigmine (Prostigmin). The authors conclude that acetylcholine affects the activity of the spinal cord, mainly through an action on interneurons.

THOMAS, Philadelphia.

ROLE OF ACETYLCHOLINE IN SYNAPTIC TRANSMISSION AT PARASYMPATHETIC GANGLIA. W. L. M. PERRY and J. TALESNIK, J. Physiol. **119**:455 (March) 1953.

Perry and Talesnik point out that there is little direct evidence for the current belief that synaptic transmission in parasympathetic ganglia is cholinergic. They attempted to provide such evidence by studying the effects of intra-arterial injection of acetylcholine and of various ganglionic-blocking agents on the ciliary ganglion. They also studied the effects of these agents on the excised, perfused cat's heart with vagus nerves attached.

The effects of acetylcholine and of blocking agents on the ciliary ganglion agreed closely with those described as occurring in the superior cervical ganglion. Since transmission in the latter is known to be cholinergic, it is reasoned that transmission in the ciliary ganglion is likewise cholinergic. In the heart small doses of acetylcholine caused inhibition; this effect is due to stimulation of intracardial ganglion cells, since the effect is blocked by nicotine and by hexamethonium. In larger doses acetylcholine also has a peripheral action on the heart. All the evidence is compatible with the hypothesis that transmission at the parasympathetic ganglionic synapse is cholinergic.

THOMAS, Philadelphia.

ELECTRICAL PROPERTIES OF CRUSTACEAN MUSCLE FIBRES. P. FATT and B. KATZ, J. Physiol. **120**:171 (April) 1953.

The electrical properties of crustacean muscle fibers were examined with the help of intracellular stimulating and recording electrodes.

The fibers have a resting potential of about 70 mv. at 20 C., the cell interior being negative to the surrounding bath. This potential difference varies with temperature (falling to about 60 mv. at 0 C.) and with the external K concentration, being about 90 mv. in K-free saline and reversing to —1 to —2 mv. in isotonic KCl solutions.

The membrane capacity of the resting muscle fibers is very large, about 40 μF per square centimeter, and their membrane resistance very small, about 100 microhms (Ω) per square centimeter. Lowering the temperature increases the membrane resistance, about 2.5 times for a change of 10 C., but has no significant effect on membrane capacity.

The electric response to a direct "cathodic" current pulse varies greatly; in many muscle fibers only small nonconducted action potentials are observed. In other fibers propagated spikes of about 60 mv. amplitude occur, rising at a maximum rate of 20 volts per second and traveling at a speed of 30 cm. per second.

When the sodium content in the muscle bath is entirely replaced by certain quaternary ammonium ions, not only is electric excitability of the muscle fibers maintained, but a large increase is observed in the amplitude and duration of electrical and mechanical responses.

Using choline as a Na substitute, the action potential attains an amplitude of 80 mv., and its wave form changes from a brief spike to a long rectangular pulse of about 25-msec. duration.

With tetraethylammonium as a Na substitute, the action potential increases to approximately 100 mv. in height and 100 msec. in duration.

With tetrabutylammonium, action potentials lasting for several seconds were recorded. The effect of tetrabutylammonium is irreversible, the enormously lengthened action potential being still obtainable when the bath has been replaced by a solution containing only calcium, magnesium, and potassium chloride and sucrose.

The following problems are discussed: (1) the interpretation of the large membrane capacity and its effect on impulse propagation, and (2) the mechanism of electric excitation of the crustacean muscle fiber, the ionic currents underlying it, and its role during normal muscle activity.

THOMAS, Philadelphia.

MEASUREMENT OF VOLUME CHANGES IN HUMAN LIMBS. R. J. WHITNEY, J. Physiol. **121**:1 (July) 1953.

A method is described for estimating changes in limb volume by measurement of changes in circumference by means of a strain gauge. The gauge consists of a length of narrow rubber tubing filled with mercury. When this is so placed as to encircle the limb, changes in limb volume will cause changes in the length of the mercury thread, hence changes in electrical resistance, which can be measured in the usual manner with a Wheatstone bridge and galvanometer. The method is based on the assumption that changes in volume are accompanied by proportionate changes in circumference. It is recognized that this is true only under certain ideal conditions, but by suitable calculations it is shown that the deviations from these conditions, encountered in practice, do not introduce important errors. Other theoretical considerations affecting the validity of the method are dealt with mathematically in an appendix. A comparison of results obtained by this method with results obtained simultaneously with a conventional plethysmograph is attempted but is not very successful, owing to mutual interference of the two methods. However, good agreement is shown with plethysmographic results obtained in separate experiments.

The method has the following advantages:

1. It permits freedom of movement of the limb and of the subject.
2. It can be compensated for temperature.
3. Readings are in percentages of limb volume; hence limb volume need not be measured.
4. The system of calibration duplicates the effect of changes in limb volume; hence it is more precise than any system of calibration applicable to a volume plethysmograph.

THOMAS, Philadelphia.

ULTRACENTRIFUGE STUDIES OF LIPOPROTEINS IN MULTIPLE SCLEROSIS. R. B. AIRD, J. W. GOFMAN, H. B. JONES, M. B. CAMPBELL, and B. GAROUTTE, Neurology **3**:22 (Jan.) 1953.

The authors present a preliminary report of ultracentrifuge studies concerned with the lipoproteins in the cerebrospinal fluid of 14 patients and in the serum of 27 patients with multiple sclerosis. They found the concentrations of the S_f (12-20) and S_f (20-100) lipoproteins in the cerebrospinal fluid were too low to be measured by means of the ultracentrifuge technique.

There may be a slight correlation between the degree of activity of the disease process and the level of lipoproteins of the S_f (12-20) types in the serum of patients with multiple sclerosis. The available data, however, were not adequate to establish this relationship as statistically significant.

ALPERS, Philadelphia.

Neuropathology

EPENDYMOMA OF THE BRAIN: PATHOLOGIC ASPECTS. H. J. SVIEN, R. F. MABON, J. W. KERNOHAN, and W. McK. CRAIG, Neurology **3**:1 (Jan.) 1953.

Svien and his colleagues describe the microscopic appearance of ependymomas. From the standpoint of cytologic architecture they divide ependymomas into four groups: the cellular, the epithelial, the myxopapillary or papillary, and the papilloma choroideum group. Except for the papilloma choroideum, the majority of ependymomas contain two, sometimes all three, types,

not only in cell characteristics, but also in their architectural patterns. Only a small number of tumors are made up of just one type. When the ependymomas are considered from the standpoint of anaplasia, they can conveniently be divided into four grades of malignancy, as previously reported by these workers.

Of the authors' series of 1,728 gliomas, 162, or 9.1%, were ependymomas. This report deals with 126 of these cases, in which the grade of malignancy could be determined. Of these, 45.2% occurred in females and 54.8% in males. Fifty-four (42.9%) occurred before the age of 14 years.

As to location, 40.5% of these ependymomas were supratentorial and 59.5% infratentorial. Tables are given summarizing the distribution of supratentorial ependymomas according to grade of malignancy and age and sex of patients. Most writers have pointed out that supratentorial ependymomas are frequently cystic. In this series, 39.2% of these tumors contained cysts. Cysts occurred in all grades of malignancy. Calcification was present in 39.2% on microscopic examination of supratentorial ependymomas.

The infratentorial tumors are also analyzed and the findings tabulated. Only 10.7% were cystic; 25.3% showed microscopic deposits of calcium.

In 19 of these cases of intracranial ependymoma, the spinal cords were available for study. In six of these cases, or 31.6%, there was implantation in the spinal subarachnoid space. It was only in those cases in which the tumor arose in the fourth ventricle that implantation occurred. Although instances have been reported in which the spinal cord implants were proved to account for clinical symptoms and findings, in none of these cases was there clinical evidence of a spinal cord lesion.

ALPERS, Philadelphia.

Meninges and Blood Vessels

SPONTANEOUS INTRACRANIAL HEMORRHAGE IN CHILDREN. W. P. RITCHIE and G. HAINES, A. M. A. Arch. Surg. **66**:452 (April) 1953.

Spontaneous intracranial hemorrhage in children originates most frequently from a congenital vascular malformation rather than from a ruptured saccular aneurysm. The precipitating role of trauma may be difficult to evaluate since children frequently incur minor head injuries. Cerebral angiography is the best diagnostic method and may reveal the specific anatomic character of the bleeding lesion. Ventriculography may be useful for localization of hemorrhage but does not permit differentiation from neoplasm. After site and source of an intracranial hemorrhage have been determined, successful surgical treatment is often possible.

The authors report in detail eight of their own observations of spontaneous intracerebral hemorrhage. In four patients the presence of an angiomatous malformation was verified; in another case the hemorrhage came from a ruptured aneurysm, but in the remaining three cases the source of bleeding remained obscure. Six of the patients recovered with little or no residual neurologic defects; two died after surgery.

LIST, Grand Rapids, Mich.

ANGIOGRAPHIC CONFIGURATION OF INTRACEREBRAL METASTATIC TUMORS. S. ETHELBERG and K. VAERNET, Radiology **61**:39 (July) 1953.

Since 1943 Ethelberg and Vaernet have obtained satisfactory cerebral angiograms on 21 patients with histologically verified cerebral metastatic tumors. From the 21 cases they have drawn conclusions concerning the identification and differential diagnosis of cerebral metastasis. Although metastatic tumors may affect any part of the brain, the commonest location is in the parietal-occipital region. Ethelberg and Vaernet believe that this localization is favored because these areas are the parts of the brain supplied by the largest terminal branches of the internal carotid artery. They believe that the usual cerebral metastasis is blood-borne and that most metastatic foci would naturally occur in the regions of the terminal arteries which are supplied by the largest vascular channels. For the same reason most cerebral metastases are cortical or are located immediately under the cortex. Endoneoplastic circulation can be demonstrated in most of these metastases. It appears as an almost circular, faintly opaque shadow in which no distinct vessel can be identified, or as a halo of delicate arteries surrounding an avascular area. One or more supplying arteries, leading directly to the endoneoplastic circulation, can usually be

identified. Displacement of adjacent cerebral arteries is minimal and extremely localized when caused by cerebral metastatic tumors. These tumors produce no change in the extracerebral vascular pattern. If multiple tumors can be demonstrated, the diagnosis of metastasis is almost certain, although multiplicity is rarely demonstrated by means of the angiogram.

Cerebral metastatic tumors must be differentiated from meningiomata and benign and malignant gliomata. Ethelberg and Vaernet believe that most cases of meningioma present little difficulty. The localization of the growth within the skull, the endoneoplastic configuration of vessels, and the relation to cerebral and extracerebral vessels are usually specific in meningioma. Meningiomata occur relatively uncommonly in the sites of predilection for cerebral metastasis.

Benign gliomata usually produce marked displacement of the major cerebral arterial trunks, leaving an almost avascular area behind. Afferent arteries cannot be identified. Abnormal vascularization within the tumor area is rare.

Malignant gliomata are characterized by the formation of irregular and abnormal blood vessels. Most malignant gliomata occur in the deep and central parts of the cerebral hemispheres rather than in the cortical areas. The abnormal area of vascularization is usually larger in malignant gliomata, and no definite afferent arteries have been demonstrated leading to it.

Ethelberg and Vaernet believe that sufficient evidence is present on angiographic studies to permit diagnosis of about two-thirds of metastatic cerebral carcinomas. When there is also good clinical evidence to suspect cerebral metastasis, the diagnosis should be considered as certain as the angiographic diagnosis of meningioma. The authors have not been able to distinguish one type of cancer metastasis from another, however.

WEILAND, Grove City, Pa.

Diseases of the Brain

POST-TRAUMATIC SUBDURAL HYDROMA. I. PERLMUTTER and R. E. STRAIN, A. M. A. Arch. Surg. **67**:122 (July) 1953.

After head injury a 50-year-old man developed progressive stupor and left hemiparesis. A right-sided subdural hydroma was evacuated, with transient improvement; but gradually a large swelling developed over the decompressive opening, which could be temporarily reduced by repeated drainage of 150 to 200 cc. of cerebrospinal fluid. Pneumoencephalography demonstrated an air and fluid level in the large subtemporal pocket.

Reoperation disclosed a large collection of colorless subdural fluid. Permanent drainage of the subdural space into the mastoid antrum was then performed by means of an inlying polyethylene tube. After this procedure, the patient rapidly improved and had remained well 10 months later.

LIST, Grand Rapids, Mich.

TUSSIVE SYNCOPE AND ITS RELATION TO EPILEPSY. D. S. O'DOHERTY, Neurology **3**:16 (Jan.) 1953.

Tussive syncope, also known as laryngeal vertigo or laryngeal epilepsy, is a syndrome in which fainting and vertigo with or without convulsions follows a paroxysm of coughing. It usually occurs in elderly men with pulmonary emphysema and a history of chronic bronchitis. O'Doherty describes five cases.

O'Doherty believes that tussive syncope with or without convulsions cannot be fully explained by the present theories of hemodynamics and abnormal vascular reflexes. It would seem that there is some other factor, such as a basic susceptibility. This is most likely an inherent abnormality of cortical function, as demonstrated by (1) incidence of this syndrome in the older age group, (2) incidence predominantly in males, (3) rarity of the syndrome despite prevalence of bronchitis and cough in the general population, (4) high percentage of abnormal electroencephalograms, (5) occasional presence of seizures independent of cough (as shown in two cases), and (6) relief of seizures, even following cough, with anticonvulsant treatment (one case).

The author concludes that tussive syncope would more accurately be classified as a symptomatic epileptic phenomenon.

ALPERS, Philadelphia.

BILATERAL ANTERIOR CINGULATE GYRUS LESIONS. R. W. BARRIS and H. R. SCHUMAN, Neurology **3**:44 (Jan.) 1953.

Barris and Schuman describe the case of a 40-year-old man who had been ill for three days prior to his hospital admission. When examined, he was mute, akinetic, indifferent to painful stimuli, and incontinent of urine. His eyes were open; deep tendon reflexes were intact; a bilateral Babinski sign was present; muscle tone was normal; he was unable to swallow foods and liquids fed to him; his pupils were of normal size, and pupillary reactions to light, both direct and consensual, were normal. Thus, by clinical standards he was unresponsive to external stimuli, yet not in coma. At necropsy bilateral lesions were found in the anterior cingulate gyri. This case is analyzed and compared with one recently reported by Nielsen and Jacobs.

Barris and Schuman feel that the symptomatology and clinical course of this condition are so characteristic as to constitute a syndrome—the syndrome of the anterior cingulate gyri. The earliest stage is characterized by apathy, akinesia, mutism, urinary incontinence, integrity of deep tendon reflexes, normal muscle tone, open eyes, physiologic pupils, indifference to pain, and bilateral Babinski sign (stage of "akinetic mutism" of Nielsen); the later stage is characterized by progressively deepening stupor, with eventual coma and death ("terminal stage" of Nielsen).

Of special interest in the case here reported were the persistently elevated temperature, pulse, and respiration rates. The authors suggest that these findings may be a reflection of a fundamental derangement in the cortical autonomic regulatory mechanisms heretofore established as being closely associated with the cingulate gyri (Area 24).

ALPERS, Philadelphia.

TUMORS INVOLVING THE CORPUS CALLOSUM. J. F. COONEY and G. S. BAKER, Proc. Staff Meet., Mayo Clin. **28**:299 (May 20) 1953.

As yet, the clinical significance of the corpus callosum has not been established entirely. Sectioning of this commissure has caused few clinical symptoms. The symptoms encountered in disorders of the corpus callosum probably are caused by direct or indirect effects on the surrounding regions of the brain, rather than to affection of the corpus callosum itself.

Cooney and Baker describe two patients who had similar pneumoencephalograms, indicative of tumors of the corpus callosum, but entirely different clinical and pathological findings.

In the first case, that of a 63-year-old man, the lesion was found to be an astrocytoma Grade 4 (glioblastoma multiforme) arising from the rostral end of the corpus callosum. The bulk of the tumor was removed for palliative relief. The second case was that of an 18-year-old girl in which exploration of the corpus callosum showed that the suspected mass was part of the cerebrum and that it was herniated through a developmental defect of the body of the corpus callosum.

In both these cases, the true nature of the lesions became apparent only after pathologic examination of tissue removed at operation. Histopathologic verification of all lesions of the brain is necessary for good management of patients who have such lesions.

ALPERS, Philadelphia.

Treatment, Neurosurgery

AEROSOL TRYPSIN IN RESPIRATORY COMPLICATIONS OF BULBAR POLIOMYELITIS: REPORT OF A CASE. C. VARGA and J. WILD, A. M. A. Am. J. Dis. Child. **86**:273 (Sept.) 1953.

A common cause of fatality in respiratory complications of acute bulbar poliomyelitis is the development of mucous plugs and atelectasis. Since treatment with aerosol enzymatic agents were effective in other diseases with these complications, it was used in a 6-year-old boy with bulbar poliomyelitis. Antibiotic aerosol therapy had been administered with intermittent positive-pressure oxygen with the Bennett unit. Because of the increasing difficulty in keeping the airway clear of tenacious mucus, aerosol trypsin (Tryptar) was aerosolized through the same apparatus. Fifty milligrams of trypsin was dissolved in 1 cc. of the Tryptar diluent and aerosolized twice a day with an oxygen flow of 6 to 8 liters per minute. Diphenhydramine hydrochloride (Benadryl) was given 10 minutes prior to each treatment. After each administration the secretions were more

fluid and more easily aspirated. In seven days the treatment was reduced to once a day and in four days discontinued. An increase in the tidal volume was noted. At a later date segmental atelectasis developed, with prompt improvement following use of aerosol trypsin. No ill effects were noted.

SIEKERT, Rochester, Minn.

SURGICAL TREATMENT OF CUSHING'S SYNDROME. M. E. JOHNSON and F. R. HARPER, A. M. A. Arch. Surg. **66**:517 (April) 1953.

Cushing's syndrome due to functional hyperactivity of the adrenal cortex is amenable to surgical treatment.

In adrenocortical hyperplasia, total adrenalectomy on one side and radical subtotal resection on the other side are recommended by the authors. Less radical procedures may lead to a recurrence of Cushing's syndrome. The bilateral operation can be accomplished in one stage by posterolateral incision with resection of the 12th rib.

In cases of adrenal neoplasm, however, a thoracic approach is preferable.

Roentgen-ray therapy of the pituitary gland often is of clinical benefit in cases of Cushing's syndrome.

The authors' conclusions are supported by a well-documented case history.

LIST, Grand Rapids, Mich.

USE OF SODIUM AMYTAL AND BENZEDRINE SULFATE IN THE SYMPTOMATIC TREATMENT OF DEPRESSIONS. JACQUES S. GOTTLIEB, Dis. Nerv. System **10**:50 (Feb.) 1949.

Gottlieb calls attention to the usefulness of the combination of amobarbital (Amytal) and amphetamine (Benzedrine) sulfate in combating manic-depressive depression and involutional melancholia. Both drugs are known to be effective antidepressants. Synergy is evident when they are given together, and the analeptic action of the amphetamine reduces the drowsiness induced by the amobarbital sodium. Another advantage has been a doubling of the duration of clinical response to amobarbital. Both medications are administered orally, in doses just short of toxic side-effects, and the regimen may usually be continued for a month before diminution of beneficial results is noted. Temporary relief was experienced by 90% of patients. In those who were mildly depressed continuation at employment was possible, and psychotherapy became more applicable. The combination of drugs was especially helpful in persons with frequent, short depressive swings, since it made it feasible for them to continue work and released them from dependence on alcohol. Moderate to severe depressions were ameliorated, and home care was eased during the period of awaiting admission to the hospital. Of 60 such patients, 14 (23%) underwent remission and did not require hospitalization. It was found that patients who had been receiving large amounts of barbiturate for insomnia had the poorest results, probably due to a tolerance factor, while those who had the medication instituted near the termination of a current attack responded the most favorably. It is felt that the drugs primarily ease the discomfort of the moderate to severe illness rather than have any effect per se on the course of the disease.

BEATON, Tucson, Ariz.

Encephalography, Ventriculography and Roentgenography

ROENTGENOGRAPHIC ASPECTS OF THROMBOSIS OF ANEURYSMS OF THE ANTERIOR COMMUNICATING AND ANTERIOR CEREBRAL ARTERIES. B. S. EPSTEIN, Am. J. Roentgenol. **70**:211 (Aug.) 1953.

The angiographic diagnosis of intracranial aneurysms has been firmly established. In most cases the aneurysm can be filled by the contrast material and be well visualized. Reports of failure of visualization caused by a proved thrombus occluding the lumen of the aneurysm are rare. Epstein reports a case in which a thrombosis was present in an aneurysm at the junction

of the anterior communicating and the anterior cerebral artery. The diagnosis was verified at autopsy. He also reports the findings in two cases in which the same x-ray signs were present and the same presumptive diagnosis was made. These patients are living and have not been operated upon; so the diagnosis has not been proved pathologically. In all three patients the plain roentgenograms of the skull were normal. Cerebral angiograms of the affected side showed a complete block of the anterior cerebral arteries at their junction with the anterior communicating arteries in all three patients. Pneumoencephalograms showed normal size, shape, and position of the ventricles in all three cases, but in each case there was evidence of a mass protruding into the cisterna chiasmatis from above. In addition to these changes the patient who died exhibited a small collection of gas in the subfrontal region. The autopsy revealed that the gas had come from the ventricular system through an infarcted and lacerated area of the frontal lobe.

WEILAND, Grove City, Pa.

INSULO-OPERCULAR ARTERIES OF THE BRAIN, WITH SPECIAL REFERENCE TO ANGIOGRAPHY OF STRIOTHALAMIC TUMORS. B. SCHLESINGER, Am. J. Roentgenol. **70**:555 (Oct.) 1953.

Schlesinger reports a single case of a striothalamic tumor (spongioneuroblastoma) in which a cerebral arteriogram, a venogram, and a ventriculogram were obtained on the patient during life and a postmortem study of the brain was made. The sylvian branches of the middle meningeal artery, in the normal subject, consist of insular segments, which course along the cortex of the island of Reil, and opercular segments, which are spread out on the surface of the frontal, parietal, and temporal lobes adjacent to the insular cortex. The term "Sylvian triangle" is proposed to designate this grouping of vessels, as seen on the lateral film of the skull taken during cerebral angiography. The Sylvian triangle as a whole is distorted, deformed, or displaced quite commonly in tumors of the frontal, parietal, and temporal lobes. The characteristic deformities of the Sylvian triangle caused by such tumors are diagrammed in Schlesinger's article. When a tumor occurs within the Sylvian fissure, this typical arterial grouping is destroyed by dissociation. In the case which Schlesinger reports, the lateral view of the cerebral arteriogram showed widening of the arch of the anterior cerebral artery and a striking separation of the arteries constituting the Sylvian triangle. The anteroposterior view of the cerebral arteriogram disclosed displacement of the anterior cerebral artery to the contralateral side and lateral displacement of the Sylvian arteries. The ventriculogram showed a large filling defect in the body of the lateral ventricle, apparently originating from below. The venogram showed an elevation of the small vein of Galen. This finding was interpreted as evidence against the possibility of the tumor being an intraventricular meningioma. Such a tumor in the lateral ventricle might normally be expected to depress the superior wall of the third ventricle and the small vein of Galen. Schlesinger felt that the arteriogram indicated an expanding lesion lying deep to the insular cortex and that the two lesions which had to be differentiated were a striothalamic glioma and an intraventricular meningioma. He felt that the venograms successfully made this differentiation.

WEILAND, Grove City, Pa.

MASSIVE DEFORMING MENINGIOMATOUS HYPEROSTOSIS. C. B. COURVILLE, C. MARSH, and P. DEEB, Bull. Los Angeles Neurol. Soc. **17**:177 (Dec.) 1952.

Courville and his colleagues describe a massive deforming tumor of the skull which was long considered by its many clinical observers to be an osteogenic sarcoma of the skull. This diagnosis was based upon the history of two previous focal injuries and the x-ray demonstration of a "sun-ray" deposition of new-formed bone in a tumor of the cranial vault, also presumed to show early signs of Paget's disease. The diagnosis of a fibrous sarcoma, based on a biopsy of the tumor, also encouraged this conclusion, which the late appearance of signs of cerebral involvement did nothing to weaken. At autopsy the relatively small mass of tumor found within the dural cavity and its active invasion of the brain, as well as a limited histological study of more cellular portions of the tumor, seemed to decide the question conclusively. Only a more critical review of numerous sections revealed the diagnosis to be meningioma.

The authors point out that massive deforming tumors of the skull are more likely to be hyperostoses provoked by underlying meningiomas than osteogenic sarcomas. This seems to be true even when the tumor is somewhat removed from the midline (where hyperostoses are more commonly located) and when signs of cerebral involvement appear late in the course of the disease, as in the case here reported.

ALPERS, Philadelphia.

CONGENITAL ABSENCE OF THE ODONTOID PROCESS. N. RASKIN, Dis. Nerv. System **14**:236-238 (Aug.) 1953.

The author reports the sixth recorded case of congenital absence of the odontoid process. The patient was a 28-year-old white woman who had suffered from generalized grand mal seizures since the age of 22. During 20 months of hospitalization her attacks became increasingly frequent, and she had periods of confusion and a long series of asthmatic paroxysms. She became progressively enfeebled and died in status epilepticus. Postmortem examination disclosed a platybasic skull with a small posterior fossa and a large foramen magnum, an atlas with a thin and atrophic anterior arch, and a large axis without an odontoid process. The occipital lobes were both undersized, the left being smaller than the right. In explanation of the association of malformations it is pointed out that the embryonic order of development of the parts involved indicates that the platybasia preceded and caused the cerebral distortion. The anterior arch of the atlas in this case was firmly attached to the unusually massive axis at the point where the odontoid process should have arisen. Hence the patient could not show the usual clinical symptoms which lead to roentgenological diagnosis of the syndrome: pain in the neck, limitation of cervical rotation, or abnormal position of the head following an accident or exercise, due to dislocation of the atlas on the axis.

BEATON, Tucson, Ariz.

LUMBOSACRAL JUNCTION. C. A. SPLITHOFF, J. A. M. A. **152**:1610 (Aug. 22) 1953.

In order to determine the relationship between the roentgenographic findings and chronic lumbar backache, a study was made comparing 100 patients with backache and an equal number of persons not bothered by backache. The routine views used for the study were anteroposterior and lateral roentgenograms of the lumbosacral spine, and a 45-degree cephalad-oblique view was utilized to visualize the fifth lumbar intervertebral disc and facets. The anomalies present, the position of the facets, the width of the fifth lumbar intervertebral disc, and the angle of the sacrum were recorded in each film.

This study demonstrated fairly conclusively that the findings on roentgenograms of the lumbosacral region of normal persons and of those with backaches are very similar. In both groups there was no significant numerical difference in the incidence of structural variation. The most frequent facet position at the lumbosacral junction was oblique or anteroposterior in both series. Osteoarthritis was present to a slightly greater extent in patients with backache. The group having backache included persons of all ages, whereas the normal group included only persons who were 40 or over. The width of the fifth lumbar intervertebral disc was approximately the same in the two groups. The measurements that were found most frequently were 15 mm. anteriorly and from 3 to 5 mm. posteriorly.

Splithoff points out that, though the findings in both groups so closely parallel each other, this does not discount the importance of routine roentgenographic study in all cases of chronic backache. The structure of the back as visualized in the film is of great importance not only in diagnosis, but also in planning treatment.

ALPERS, Philadelphia.

CLEIDOCRANIAL DYSOSTOSIS. D. EISEN, Radiology **61**:21 (July) 1953.

Cleidocranial dysostosis was first established as a clinical and pathological entity in 1898. Eisen adds the report of four cases to the literature.

Cleidocranial dysostosis is a congenital abnormality of the skeletal system, particularly involving bone that develops in membrane. The entire skeleton is usually affected to some degree, although the pathognomonic changes are in the clavicles and the skull. Posteroanterior roent-

genograms of these patients' skulls show a shape suggesting an inverted pear. The skull has abnormal width and prominent frontal and parietal bosses. The fontanelles are wide and show delayed closure. All four of Eisen's cases showed a persistent metopic suture with wide separation of the upper part. None of his four patients showed ossification of the nasal bones. The defects in the clavicle may vary from complete absence of both clavicles to a small defect in one clavicle. Oftenest the outer ends of the clavicles are undeveloped or exist as separate centers of ossification which are not fused with the inner ends of the clavicles.

Retarded ossification of the epiphyses of all bones is common in cleidocranial dysostosis. The permanent teeth often show late eruption, impaction, and malocclusion. A number of less constant abnormalities of various bones are described as occurring in the author's cases.

WEILAND, Grove City, Pa.

CONGENITAL HEREDITARY CRANIUM BIFIDUM OCCULTUM FRONTALIS. R. J. TERRAFRANCA and A. ZELLIS, Radiology **61**:60 (July) 1953.

Terrafranca and Zellis report four cases of cranium bifidum occultum frontalis which occurred in three generations of an American Negro family. The first patient was a 6-year-old girl, whose skull was x-rayed because she had fallen and struck her head and clinical examination had revealed no sensation of bone resistance in the middle portion of the forehead. Roentgenograms of the skull revealed a large symmetrical defect in the middle of the frontal bone. The defect was shaped like a shield, and short segments of a metopic suture were seen above and below the defect. Because of this finding, the patient's brother and mother were examined. The boy was 14 years of age. Roentgenograms of his skull showed a similar, but smaller, defect in the middle portion of the frontal bone. Again, there was a metopic suture above and below the defect. The mother was 37 and stated that both she and her mother had had "soft spots" in the forehead, which had "gotten hard" as they grew older. Roentgenograms of the mother's skull showed a small area of decreased density in the midfrontal region which was shaped like a U. The fourth case was the maternal grandmother, who was dead and who had never had her skull examined, but who was included in this report because of the history of a "soft spot" in the frontal region.

Terrafranca and Zellis believe that these defects represent persistent large metopic fontanelles, which gradually close from above as the patients grow older. They believe that the large defect in the little girl's skull will in time become a small one, probably in the shape of a U, like the one seen in the mother's skull. They have no proof of this theory, but they believe it logical since the youngest patient had the largest defect and the oldest patient had the smallest. The history of the "soft spots" becoming hard tends to substantiate the theory.

WEILAND, Grove City, Pa.

PNEUMOENCEPHALOGRAPHIC STUDIES FOLLOWING COMPLETE REMOVAL OF SUPRATENTORIAL LESIONS. A. J. BELLER and A. SCHWARTZ, Radiology **61**:200 (Aug.) 1953.

Beller and Schwartz have obtained pneumoencephalograms before and after surgical removal of encapsulated supratentorial intracranial mass lesions in 10 cases. In three cases the diagnosis was meningioma; in five, brain abscess; in one, Echinococcus cyst; and in one, oligodendroglioma. All patients showed a shift of the ventricular system away from the midline in the preoperative films, and all showed a return of the displaced ventricular system to the midline in the postoperative films. The pneumoencephalograms obtained after operation showed symmetrical dilatation of the ventricular system in all three cases of meningioma and in two of the cases of brain abscess. The other cases all showed asymmetrical dilatation of the ventricular system to some degree. No filling of the subarachnoid spaces was obtained in the preoperative pneumoencephalograms in six patients. However, filling of the subarachnoid spaces was obtained after operation in 9 of the 10 cases.

WEILAND, Grove City, Pa.

SPONTANEOUS FRACTURE OF THE FEMUR IN AN INFANT WITH A LARGE OCCIPITAL MENINGOCELE. A. JUNGMANN, Radiology **61**:231 (Aug.) 1953.

Jungmann discusses previous reports by Caffey, Smith, Lis, and Frauenberger, who have described cases of fractures of the bones of children with subdural hematomas when no known trauma has been involved. Multiple fractures of the long bones frequently occur after little or no trauma in young patients with subdural hematoma. Subdural hematoma has been suspected on finding such fractures and were subsequently found to be present. Jungmann reports the case of a child 11 months old who was hospitalized for diarrhea. During the child's hospital stay she suffered a fracture of the left femur. No known trauma was involved. A week later the child died of bilateral bronchopneumonia. At autopsy it was found that the fracture of the femur had occurred through a normal area of bone and had been healing in a normal manner. The patient had no subdural hematoma, but she had an occipital meningocele, which communicated with the cisterna magna. Jungmann suggests that different types of intracranial abnormalities may predispose to fractures of the long bones in some manner as yet unknown.

WEILAND, Grove City, Pa.

BASILAR IMPRESSION AND PLATYBASIA IN PAGET'S DISEASE. M. H. POPPEL, H. G. JACOBSON, B. K. DUFF, and C. GOTTLIEB, Radiology **61**:639 (Oct.) 1953.

Poppel and his associates studied skull roentgenograms of 75 patients for whom the roentgen diagnosis of Paget's disease of the skull had been made. One hundred two consecutive skull x-rays which were roentgenographically normal were studied for comparison with the 75 abnormal ones. The authors conclude that basilar impression and platybasia are two different entities and have no direct relationship with each other. Basilar impression is an abnormal cephalad invagination of the region of the foramen magnum of the skull. Platybasia is an abnormal obtuseness of the basal angle of the skull.

Basilar impression is measured by the relationship of the tip of the odontoid process of the second cervical vertebra to Chamberlain's line. This line is drawn on the lateral roentgenogram of the skull from the posterior margin of the hard palate to the posterior margin of the foramen magnum. In this study the average normal position for the tip of the odontoid process was about on Chamberlain's line. In this series of cases a difference of 6.6 mm. between the tip of the odontoid process and the line, whether the odontoid was above or below the line, was considered a statistically significant deviation from the mean. Twenty-seven of the 75 cases of Paget's disease of the skull showed such a deviation, and in all these 27 cases the odontoid tip lay above Chamberlain's line.

The basal angle of the human skull is also determined from a lateral roentgenogram of the skull. A line is drawn from the nasion to the center of the sella turcica. Another line is drawn from the center of the sella turcica to the anterior margin of the foramen magnum. The angle formed at the junction of these two lines is called the basal angle. The average human basal angle is 135 degrees. The normal minimum is about 121 degrees, and the normal maximum is about 152 degrees. No significant statistical difference was found in the basal angle between the normal skull x-rays and the ones showing Paget's disease. The conclusion reached is that basilar invagination is frequent with Paget's disease of the skull but that platybasia is not frequent.

The clinical manifestations of basilar impression resemble those of the Arnold-Chiari syndrome, syringomyelia, amyotrophic lateral sclerosis, tumor, or any other disease causing high compression of the spinal cord. Basilar impression must be thought of as a diagnostic possibility when such symptoms exist.

WEILAND, Grove City, Pa.

DETECTION OF INTRAOCULAR TUMORS WITH THE USE OF RADIOACTIVE PHOSPHORUS. J. S. KROHMER, C. I. THOMAS, J. P. STORAASLI, and H. L. FRIEDELL, Radiology **61**:916 (Dec.) 1953.

A number of cases of detachment of the retina present a difficult problem in differential diagnosis. If a tumor is suspected as the cause of the detachment, enucleation is necessary, for the interior of the eye cannot be subjected to biopsy. Krohmer, Thomas, Storaasli, and Friedell have

found that tumors of the eye take up more radioactive phosphorus than normal ocular tissue does. This fact makes possible the diagnosis of anterior tumors of the eye by using radioactive phosphorus and counting the uptake over various portions of the eye. Radioactive phosphorus is a beta emitter, and the range of the beta particles in human tissue is about 8 mm. For this reason the diagnosis of posterior tumors of the eye is more difficult. The authors feel that the results are less certain in these cases. They report on 32 cases of various intraocular lesions which they have studied by using the radioactive phosphorus technique. The technique is considered an adjunct to careful clinical evaluation rather than a conclusive diagnostic test, for the location of the suspected tumor must be ascertained rather accurately by a careful ophthalmoscopic examination before counting the uptake of the radioactive phosphorus.

The patient is given a dose of 500 μc of radioactive phosphorus intravenously. Counting is begun immediately with a special Geiger-Müller tube placed in contact with the eyeball. Counting is also done one-half hour and one hour after administration of the phosphorus. The ratio of uptake in the tumor region as compared with the uptake in a normal region of the same eye is plotted for each study. A ratio greater than 1.4:1 suggests a tumor located anteriorly. A ratio greater than 1.2:1, but less than 1.4:1, may suggest a posterior tumor, but more work must be done concerning this finding. A ratio less than 1.2:1 usually signifies no tumor. Nine anterior tumors were diagnosed by this method, and in seven cases the diagnosis was confirmed by histologic study of the enucleated eye. These seven cases all had melanoma or melanosarcoma of the choroid. In two of the nine cases the diagnosis was not verified because the tumor was thought to be metastatic carcinoma from the breast, and the eye was not removed.

Three posterior tumors were diagnosed by this method. In all three cases the diagnosis proved to be correct. In 14 cases the diagnosis of no tumor was made. In 4 of these operation was performed and no tumor was found. The rest have followed a clinical course suggesting that no tumor is present.

WEILAND, Grove City, Pa.

News and Comment

ANNOUNCEMENTS

The Walter E. Fernald State School, Waverley, Mass., has a training grant in psychiatry under the National Mental Health Act, Department of Health, Education and Welfare, for a Federal Fellowship position from July 1, 1954 to June 30, 1955.

The position offers ample opportunity for studying the clinical and pathological aspects of mental deficiency and child psychiatry in general. The trainee participates in the large outpatient clinic and in many special activities in Boston in the line of child psychiatry. The position offers a unique opportunity to participate in the study of the large neuropathological material available at this institution, to receive training in neuropathology and, if so desired, to conduct some specific research.

INSTITUTE OF PSYCHIATRIC TREATMENT

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Registration fee, $35. Address correspondence to Dr. Leo Alexander, 433 Marlborough St., Boston.

NATHAN SAVITSKY LABORATORY IN NEURO-PHYSIOLOGY

A great loss was sustained by the untimely passing of Dr. Nathan Savitsky. To honor the memory of this outstanding neuropsychiatrist, scholar, and humanitarian, funds are being collected for the establishment of a Nathan Savitsky Laboratory in Neuro-Physiology at the Albert Einstein College of Medicine (now under construction) of Yeshiva University. Communications should be addressed to Dr. W. Karliner, 270 Park Ave., Bldg. A., Room 717, New York.

INDEXES

This issue of the ARCHIVES appears in two parts, the second of which is the index for the preceding volume. To make the index more usable to the readers and to enable them to find information with less difficulty than has been encountered in previous volumes, the index has been broken down into three separate indexes: Title Index, Author Index, and Subject Index. The Title Index, which will take the place of the six-month Table of Contents, previously published with the index of the journals, has been prepared in such form that it can be separated from the other indexes and bound in the front of the volume. It consists of the titles of the articles arranged in alphabetical order and accompanied by the name of the author, the name of the senior author if there are more than two, the names of both authors if there are two, and the page number on which the article begins. The Author Index contains the names of all authors of articles appearing in the ARCHIVES and of the presenters of cases or papers before societies. The third index, the Subject Index, contains in alphabetical order the important subjects which have been dealt with in the volume. Individual abstracts are no longer indexed; only the categories under which they have been classified are listed. Book Notices and news items are included in this Index.

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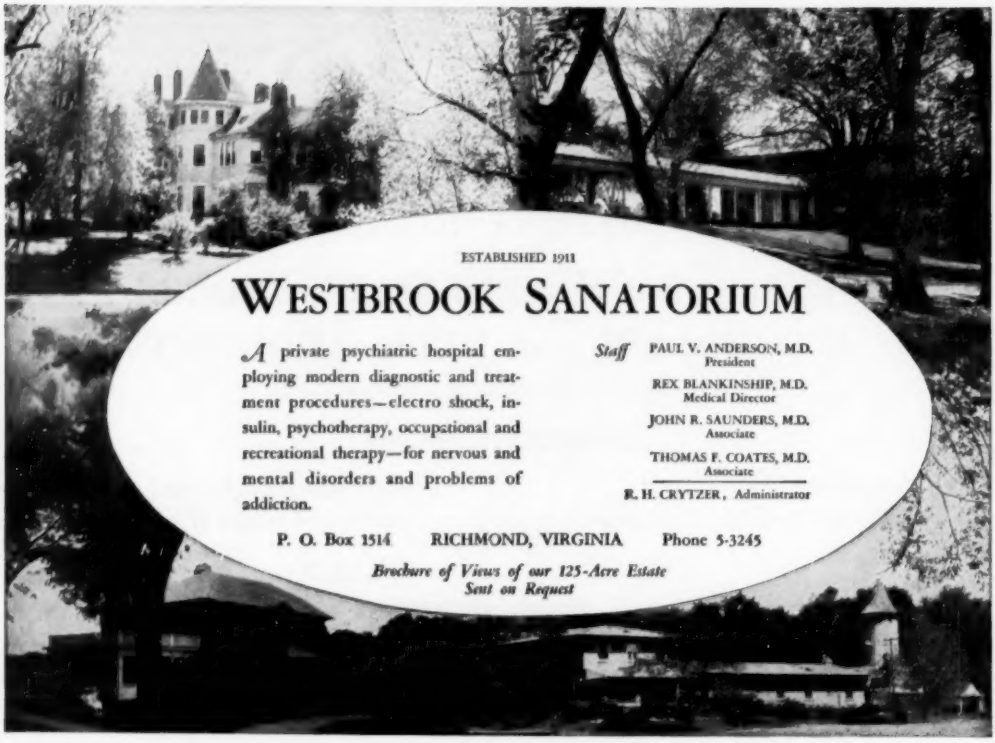
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